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# JOURNAL OF THE CHEMICAL SOCIETY

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The Chemical Society was founded in 1841 and received a Royal Charter in 1848.

The main function of the Society is to foster original research in Chemistry and to facilitate the discussion and dissemination of new knowledge in all branches of the science.

### FELLOWSHIP

Fellowship of the Chemical Society is open to men and women of all nationalities who are interested in Chemistry and wish to keep in touch with its advances. Fellows are elected by the Council.

### PRIVILEGES

Fellows who pay the annual subscription of £3 have the following privileges

1. To receive any three of the following publications of the Society without extra charge
   *Journal of the Chemical Society.*
   *British Chemical and Physiological Abstracts* "*AI*," "*AII*," *or* "*AIII*."
   *Annual Reports on the Progress of Chemistry.*
   *Reprints of Lectures published in the Journal.*

   One copy of the Abstracts "A" Index and of Abstracts C (Analysis and Apparatus) are supplied to Fellows receiving one or more sections of the Abstracts. Publications in excess of the three allowed can be purchased at schedule prices.
2. To consult and borrow the books in the Library (45,600 volumes).
3. To attend meetings of the Society both in London and outside London, and to introduce two guests thereto.
4. To apply for research grants.
5. To submit original papers for publication in the *Journal.*

Fellows under the age of 25, who so wish, may pay an annual subscription of £1 10s. and receive until the end of the year in which they reach that age:

The *Annual Reports on the Progress of Chemistry*, and either the *Journal of the Chemical Society* or two sections of *British Chemical and Physiological Abstracts A*.

Such Fellows receive no other publications of the Society, but enjoy all the other privileges accorded to those paying the full annual subscription.

### PUBLICATIONS

(*a*) *The Journal of the Chemical Society*, which is published monthly, contains the results of investigations which cover the whole field of pure chemistry.

(*b*) *British Chemical and Physiological Abstracts.*

The Society collaborates with the Society of Chemical Industry, the Physiological Society, and the Biochemical Society in contributing to the maintenance of the Bureau of Abstracts, which issues every month abstracts of papers dealing with all branches of pure and applied chemistry and physiology published in all parts of the world.

*British Chemical and Physiological Abstracts A* is divided into three sections: AI, General, Physical and Inorganic Chemistry; AII, Organic Chemistry; AIII, Physiology and Biochemistry, including Anatomy.

(*c*) *Annual Reports on the Progress of Chemistry.* These reports, written by experts, summarise the important new advances in pure chemistry and related subjects.

### LIBRARY

The extensive reference and lending library of the Chemical Society contains over 45,600 volumes dealing with every aspect of Chemistry and with many branches of related sciences. The Library is open on Monday to Friday from 10 a.m. to 6 p.m., and from 10 a.m. to 5 p.m. on Saturdays.

### MEETINGS

(*a*) *In London.*

Scientific Meetings of the Society are held usually on the first and third Thursdays of each month from October to June at Burlington House, at which papers dealing with original work are read and discussed, organised discussions on subjects of current interest are arranged, and lectures by eminent British and foreign chemists are delivered.

(*b*) *Outside London.*

Scientific Meetings and lectures are also held outside London, and form an important part of the activities of the Society in the Provinces.

### RESEARCH FUND

A Research Fund is available for the assistance of chemical research, and sums amounting annually to about £700 are granted for this purpose. Application for grants must be made on the appropriate form, which may be obtained from the General Secretary.

Forms of Application for Fellowship can be obtained from THE GENERAL SECRETARY, THE CHEMICAL SOCIETY, BURLINGTON HOUSE, PICCADILLY, LONDON, W.1.

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# THE CHEMICAL SOCIETY

## NOTICE OF FORTHCOMING SCIENTIFIC MEETINGS

*LONDON.*

*Thursday, April 4th, 1946, at 2.30 p.m.*

Discussion, **Some Aspects of the Chemistry of Macromolecules,** arranged by Professor H. W. Melville, Ph.D., D.Sc., F.R.S., to be held at the Institution of Mechanical Engineers, Storey's Gate, St. James's Park, London, S.W. 1.

The following contributions will be made :

"Low-temperature polymerisation processes." By Professor M. Polanyi, Ph.D., M.D., F.R.S.
"Aqueous phase polymerisation of vinyl compounds." By Professor M. G. Evans, D.Sc.
"Kinetics of polymerisation of vinyl compounds in the gas and liquid phases." By Professor H. W. Melville, Ph.D., D.Sc., F.R.S.
"Equilibrium properties of high polymer solutions and gels." By Dr. Geoffrey Gee, M.Sc., Ph.D., A.R.I.C.
"The study of macro-molecules by infra-red spectroscopy." By Dr. H. W. Thompson, M.A., B.Sc., D.Phil.
"The study of high polymer structure by X-ray diffraction methods." By Mr. C. W. Bunn, M.A., B.Sc.

(A limited number of pre-prints of the above contributions are available and can be obtained by Fellows from the General Secretary.)

*BIRMINGHAM.*

*Thursday, April 25th, 1946.*

**The Hundred and Fifth Annual General Meeting of the Chemical Society** will be held at the University of Birmingham on April 25th, 1946. At 12 noon the business portion will be held, followed by a reception and luncheon at the University at 1 p.m. At 3 p.m. the presentation to Mr. S. E. Carr will be made, followed by the Presidential Address and installation of the new President. Full particulars will be circulated to Fellows later.

*EDINBURGH.*

*Friday, March 22nd, 1946, at 7.30 p.m.*

Lecture, **Trace Elements in Agriculture,** by Dr. W. G. Ogg, M.A., Director of the Rothamsted Experimental Station.

Joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the North British Station Hotel.

*MANCHESTER.*

*Thursday, March 14th, 1946, at 5 p.m.*

Meeting for the reading of the following papers :

"The diffusion of dyes into an absorbing medium." By H. A. Standing and J. O. Warwicker.
"The pyrolysis of organic compounds. Preparation of some conjugated diolefines." By H. Gudgeon, R. Hill, and E. Isaacs.
"Aspergillic Acid. Total synthesis of a racemic 2′-hydroxy-3 : 6′-di*sec*butylpyrazine and its relationship to deoxyaspergillic acid." By G. T. Newbold and F. S. Spring.
"Experiments on the Scholl reaction." By G. Baddeley and J. Kenner.

To be held in the Chemistry Lecture Theatre of the University.

*Thursday, May 2nd, 1946, at 6 p.m.*

Lecture, **Recent Developments in Polynucleotide Chemistry,** by Professor J. M. Gulland, D.Sc., F.R.S.

To be held in the Chemistry Lecture Theatre of the University.

*NEWCASTLE AND DURHAM.*

*Friday, May 10th, 1946, at 5.30 p.m.*

Bedson Club Lecture, **Whither Chemistry ?** by Sir Robert Pickard, D.Sc., Ph.D., F.R.S.

To be held in King's College, Newcastle-on-Tyne, and all Fellows are invited.

*SHEFFIELD.*

*Friday, May 3rd, 1946, at 5.30 p.m.*

Lecture, **Vitamin A,** by Professor R. A. Morton, D.Sc., F.R.I.C.

Joint meeting with the University Chemical Society, to be held in the Chemistry Lecture Theatre of the University.

*SOUTHAMPTON.*

*Friday, May 3rd, 1946, at 5 p.m.*

Lecture, **The Chemistry of Penicillin,** by Sir Ian Heilbron, D.S.O., D.Sc., LL.D., F.R.S.

*Friday, May 17th, 1946, at 5 p.m.*

Lecture, **Nucleoproteins,** by Professor J. M. Gulland, D.Sc., F.R.S.

*Friday, May 24th, 1946, at 5 p.m.*

Lecture, **Structural Inorganic Chemistry,** by Professor W. Wardlaw, D.Sc., F.R.I.C.

Joint meetings with the University College Chemical Society to be held in the Physics Lecture Theatre of University College.

# PROCEEDINGS

OF THE

# CHEMICAL SOCIETY.

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**Minutes of a**

**SCIENTIFIC MEETING**

**held at Burlington House, Piccadilly, W. 1, on Thursday, February 7th, 1946, at 5 p.m.**

The President, PROFESSOR W. N. HAWORTH, D.Sc., F.R.S., was in the Chair.

**MINUTES.**

The minutes of the Scientific Meeting held on January 17th, 1946, were taken as read and signed.

**FORMAL ADMISSION OF FELLOWS.**

The following were admitted Fellows of the Chemical Society: J. A. R. MacLean, W. W. Cuthbertson, K. A. Wickham, F. Clark.

**SCIENTIFIC COMMUNICATIONS.**

The following papers were read and discussed:

"Synthetic Antimalarials." By F. H. S. Curd, F. L. Rose, and co-workers.
"Amorphous Carbon." By J. Gibson, M. Holohan, and H. L. Riley.

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## OFFICIAL ANNOUNCEMENTS

**DEATHS.**

The Council regret to announce the deaths of the following Fellows:

| | Elected. | Died. |
|---|---|---|
| Theodore Edward Archard (Boston, Lincs.) | 1941 | Reported missing, presumed killed. |
| Biraj Mohan Gupta (Lucknow) | 1920 | May 26th, 1945. |
| Kapilram Hardevram Vakil (Bombay) | 1911 | January, 1946. |
| Sydney Martineau (London) | 1887 | Jan. 15th, 1945. |
| Joseph William Patterson (Durham) | 1896 | Jan. 15th, 1946. |
| William Pollard (Devon) | 1898 | Jan. 20th, 1946. |
| Ernest George Radley (London) | 1920 | Dec. 7th, 1945. |
| Frederick Gwilym Treharne (Bournemouth) | 1895 | Jan. 17th, 1946. |
| Frederick Edward Twining (California, U.S.A.) | 1942 | Oct. 18th, 1945. |
| James Watt (Edinburgh) | 1945 | Jan. 3rd, 1946. |

**ACKNOWLEDGMENTS.**

The thanks of the Council have been conveyed to Professor E. D. Hughes for a contribution to the Research Fund, and to Mr. H. A. Auden for presenting publications of the Society.

**NOMINATIONS FOR VACANT PLACES ON THE COUNCIL.**

The following is the list of nominations for the new Council:

**President.** (*One vacancy.*)

CYRIL N. HINSHELWOOD.

**Honorary Secretaries.** (*Two vacancies.*)

DONALD H. HEY.
JOHN L. SIMONSEN.

**Vice-Presidents who have not filled the Office of President.** (*Two vacancies.*)

FREDERICK CHALLENGER (Leeds).
REGINALD P. LINSTEAD (Teddington).
SAMUEL SUGDEN (London).

**Ordinary Members of Council.**

**Constituency I. (South-East England.)** (*Four vacancies.*)

ALBERT E. ALEXANDER (Cambridge).
JOHN F. J. DIPPY (London).
JOHN G. A. GRIFFITHS (London).
STANLEY H. HARPER (Southampton).
FRANK E. KING (Oxford).
FREDERICK G. MANN (Cambridge).
CHARLES W. SHOPPEE (London).

**Constituency III. (North-West England, North Wales, and the Isle of Man.)** (*Three vacancies.*)

DOUGLAS W. HILL (Manchester).
ALEXANDER MCGOOKIN (Liverpool).
MICHAEL POLANYI (Manchester).

**Constituency V. (Scotland.)** (*One vacancy.*)

HARRY W. MELVILLE (Aberdeen).

**APPEAL FOR COPIES OF THE SOCIETY'S PUBLICATIONS FOR LIBERATED EUROPEAN COUNTRIES.**

The Society has been invited to make sets of its publications available for free distribution to important centres in allied countries. Owing to wartime restrictions, the Society is unable to provide sufficient copies of its publications issued during the war years 1940—1945. The Council has, therefore, decided to appeal to Fellows for further copies of the *Journal*, *Annual Reports*, and *Abstracts* for those years. Any Fellow who is willing to provide such publications for this purpose is invited to notify the General Secretary as soon as possible. No publications should be sent at this stage.

**SCIENTIFIC MEETINGS AT BURLINGTON HOUSE.**

Owing to the limited accommodation and large attendance at the Society's Scientific Meetings, the Council has decided that in future only Fellows and guests accompanying Fellows will be admitted to the Lecture Room, and whilst other visitors introduced by Fellows will be welcome, if accommodation permits, they will not be admitted to the Lecture Room until five minutes before the Lecture was due to begin.

**ADVISORY SUB-COMMITTEE ON NOMENCLATURE.**

An Advisory Sub-Committee, with representatives appointed by the Bureau of Abstracts, has been formed to advise on questions of chemical nomenclature.

**BRITISH STANDARD SPECIFICATIONS.**

The following drafts have been received for technical comment :

CH(PVC) 3299. Ready mixed paints.
(*a*) CH(PVC) 3047. Water paints and distempers.
(*b*) CH(PVC) 3383. Knotting.

These have been placed in the Library and Fellows wishing to make technical comment are requested to do so before March 29th, 1946, to the British Standards Institution, 28, Victoria Street, Westminster, S.W. 1.

**ELECTION OF NEW FELLOWS.**

The following 77 candidates were elected Fellows of the Chemical Society on February 7th, 1946 :

Margaret Mary Adams.
Carl Rupert Addinall.
Abdul Ahad.
Norman Albon.
Sydney Hubert Bannister.
Harold Randall Barnard.
Edward Arthur Bassett.
Ethel Irene Beeching.
Armin Blumenthal.
Donald Bramley.
Arnold Leslie John Buckle.
Douglas Norton Buttrey.
Albert Gordon Caldwell.
John Russell Carter.
John Evelyn Cave-Browne-Cave.
George William Cherry.
Victor Malcolm Clark.
Raymond Cobb.
Geoffrey William Dakin.
Henry Conrad Dunn.
Constantin Edeleanu.
David George Malcolm Eve.
Hugh McNair Farquhar.
Maurice Ernest Foss.
Stanley Arthur Frapwell.
Helen Frenkel.
Jervis Moisson Fulmer.

Robert Howard Gammon.
Neville Allan Gibson.
Andre Givaudan.
Geoffrey Frederick Glover.
George Victor Hancock Grimmett.
John Gruschka.
Eric Joseph Gunn.
Frank Hall.
Shirley Phillimore Harrold.
Alfred Herzka.
Kenneth John Hill.
Alan Rowland Hine.
Henry Allen Hodge.
George Robert Jenkinson.
Geoffrey Kempson Jones.
Shirley Wickham Jones.
Denis Alfred Alexander Kidd.
Douglas Stanley Lewis.
Anthony Duncan Littlewood.
Allan Maccoll.
William Mallinson McIsaac.
Geoffrey Walsh Meadows.
Hemant Kumar Moyade.
John Munro.
Kenneth Cecil Murfitt.
Charles Christopher Oglethorpe.
Jean Margaret Palmer.
George Frederick Perry Parsons.
Alfred Holgate Raine.
Bernard Raistrick.
Srinivasa Rajagopalan.
Walter Jacob Rosenfelder.
David John Michel Rowe.
Alexander Bilton Roy.
Olga Rutherford.
Aldo Santi.
Alan George Sharpe.
William Dring Southam.
Anthony Sparks.
Chester Merle Suter.
Eric Malcolm Thain.
Reginald William Thomas.
George Henry Tweddell.
Norbert Uri.
Harold Vagtborg.
Arthur Philip Wade.
Stephen Collier Wallwork.
Norman Frank Warren.
Gerald Hugh Watson.
Norman Edgar Williams.

## MEETINGS OUTSIDE LONDON.

*SOUTH WALES.*

"The Separation of Isotopes and Thermal Diffusion," by Professor James Kendall, D.Sc., F.R.S.

A meeting of the Chemical Society was held jointly with the University College of Swansea Chemical Society on January 28th, 1946, in the Chemistry Lecture Theatre, University College, Swansea, the Chair being taken by Professor J. E. Coates, the Local Representative. In his lecture, Professor Kendall dealt mainly with his own researches in this field. A technique was developed by which ions of different elements in aqueous solution having specific mobilities differing by as little as one per cent. could be completely separated, but no separation of isotopic ions of metals could be effected, indicating identity of mobility. After describing his original idea and early experiments for isotopic separation at an electrode in electrolysis and the first success by this method achieved by G. N. Lewis in the separation of deuterium, Professor Kendall discussed the method of thermal diffusion in gas mixtures and in solutions and showed some striking experiments to illustrate both.

After a discussion in which Messrs. H. R. Forman, G. E. Coates, E. Thornton, and Professor F. L. Jones took part, a vote of thanks to the lecturer was proposed by Dr. N. H. Hartshorne, seconded by Mr. M. H. Roberts and carried enthusiastically.

## LIST OF APPLICATIONS FOR FELLOWSHIP

(*Fellows wishing to lodge objections to the election of these candidates should communicate with the Honorary Secretaries before March 31st, 1946. Such objections will be treated as confidential. The forms of application are displayed in the Library.*)

***Adams, David Hemsley,** B.Sc. (Lond.), A.R.I.C. British. 4, Carlyon Close, Wembley. Research Chemist. *Signed by :* W. Davey, J. A. Pickard, R. C. Chirnside.

**Allen, Russell James Laurence,** B.Sc. (W. Australia), M.Sc. (Melbourne), Ph.D. (Cantab.), A.R.I.C. British. Monkhouse and Glasscock, Ltd., Snowfields, S.E. 1. Chief Chemist. *Signed by :* John W. Corran, A. L. Bacharach, Mamie Olliver.

***Bailes, Peter,** B.Sc. (Lond.). British. Stepaside, Church Avenue, Farnborough. Junior Scientific Officer employed by Ministry of Aircraft Production. *Signed by :* Brian A. Loveridge, J. A. Wrenn, R. J. W. Le Fèvre.

***Baillie, Thomas William Terence,** M.Sc. (Q.U.B.), A.R.I.C. British. Garryowen, 37, Stormont Park, Knock, Belfast. Assistant Lecturer in Chemistry, Queen's University, Belfast. *Signed by :* A. R. Ubbelohde, H. Graham, R. C. Pink.

***Boud, Alan Hugh,** B.Sc. (Lond.). British. c/o Mrs. Pullen, 74, Westbrook Road, Heston. Physical Chemist in New Products Division, The Pyrene Co., Ltd. *Signed by :* J. Masson Gulland, D. O. Jordan, W. J. Clifford.

**Bourquin, Jean-Pierre,** Dip.Chem.Eng. and D.Chem. (Zürich). Swiss. 157, Oberwilerstrasse, Basel. Research Chemist, c/o F. Hoffman–La Roche and Co., Basel. *Signed by :* P. Karrer, T. Reichstein, V. Prelog.

**Bradford, Eric Andrew,** A.R.I.C. British. 61, Knockhall Road, Greenhithe. Development Chemist in the Paper Industry. *Signed by :* S. R. H. Edge, R. Leslie Collett, H. J. T. Ellingham.

**Brasher, Dora Mary,** B.Sc. (Lond.), A.R.I.C. British. 66, Woodstock Road, Bedford Park, W. 4. Research Chemist. *Signed by :* F. Wormwell, W. H. J. Vernon, R. St. J. Preston.

**Brightwell, Stanley Thomas Patrick,** M.Sc. (Lond.), A.R.I.C., D.I.C. British. Dovecot, Kingston, Cambridge. Food Chemist, Messrs. Sainsbury, Stanford Street, S.E. 1. *Signed by :* Alex. Findlay, H. J. T. Ellingham, R. Leslie Collett.

**Brown, Arthur William,** B.Sc. (L'pool), A.R.I.C. British. 29, Park Avenue, Eccleston Park, Prescot. Assistant Analytical Chemist, Associated Portland Cement Manufacturer, Ltd. (Central Laboratories). *Signed by :* W. A. Snow, H. F. S. Rogans, J. Stewart Cook.

**Bull, Arthur William,** B.Sc. and B.Pharm. (Lond.), A.R.I.C., Ph.C., M.P.S. British. 21, Derby Road, Beeston. Development of Pharmaceutical and Medicinal Products. *Signed by :* A. D. Powell, W. F. Elvidge, John C. Roberts.

**Cathro, James,** A.R.I.C. British. 24, Clyde Street, Carluke. Works Chemist, R. and W. Scott, Ltd., Preserve Manufacturers, Carluke. *Signed by :* A. B. Crawford, Ezra Golombok, Henry G. A. Anderson.

**Chalmers, John Ritchie.** Passed final examination for B.Sc. (St. Andrews). British. 10, Duke Street, Hawick. Chemist, L. Light & Co., Ltd., Old Bowry Laboratories, Wraysbury. *Signed by :* John Dewar, J. C. Irvine, John Read.

***Chapman, Cyril Norman.** National Certificate in Chemistry. British. 25, Belvoir Road, Bristol, 6. Medical Laboratory Technician, Department of Preventive Medicine, University of Bristol. *Signed by :* W. P. Thistlethwaite, J. Bridges, Arthur Marsden.

**Clark, George Alexander Sutton,** B.Sc.Hons. and A.R.T.C. (Glas.), A.R.I.C. British. Dalton Grange, Huddersfield. Works Chemist, I.C.I. Dyestuffs Division. *Signed by :* Robert Raw, E. J. Hemer, Thos. A. Simmons.

**Clark, Norman Owen,** M.Sc. and Ph.D. (Lond.), D.I.C., A.R.C.S. British. 35, Beauford Way, Ewell. Scientific Officer, Chemical Research Laboratory, D.S.I.R. *Signed by :* W. H. J. Vernon, N. E. Topp, G. E. Little.

**Collins, William Thomas,** M.Sc. (Wales), A.R.I.C. British. Ravensmead, Gillas Lane, Houghton-le-Spring, Co. Durham. Schoolmaster. *Signed by :* C. W. Gibby, G. H. Christie, J. E. Coates.

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## PAPERS RECEIVED

List of papers received between January 4th and February 7th, 1946. (This list does not include the titles of papers which have been read at a Scientific Meeting or which have appeared in the *Journal.*)

" Podocarpic acid. Synthesis of 1 : 12-dimethyl-6- and -7-methoxyoctahydrophenanthrene-1-carboxylic acids." By R. D. HAWORTH and B. P. MOORE.

" Syntheses of 9-substituted flavines as antimalarials." By M. M. NEEMAN.

" New syntheses of heterocyclic compounds. Part VI. Triazafluorenes and azaphenazines from 3 : 5-dinitrochloropyridine." By V. A. PETROW and J. SAPER.

" An alternative route to stilboestrol." By A. E. WILDER SMITH.

" The effect of steric hindrance on the course of Pfitzinger's reactions." By NG. PH. BUU-HOI.

" Vapour pressure of phthalic anhydride." By D. A. CROOKS and (MISS) F. M. FEETHAM.

" The preparation of 4-aminophenylsulphones. Part I. The reaction between aromatic sulphinic acids and quinones or quinone-imines." By S. PICKHOLZ.

" Methylation of β-methyl glucopyranoside and αβ-methyl xylopyranosides by thallous hydroxide and methyl iodide." By C. C. BARKER, E. L. HIRST, and J. K. N. JONES.

" Attempts to find new chemotherapeutic amidines. Part III. Nuclear-substituted derivatives of 4 : 4′- and 3 : 3′-diamidinostilbene." By J. N. ASHLEY and J. O. HARRIS.

" The preparation of *ortho-* and *para-*nitroacetophenone." By A. H. FORD-MOORE and H. N. RYDON.

" Kinetics of the halogenation of acetone in alkaline solutions." By R. P. BELL and H. C. LONGUET-HIGGINS.

" The methyl thioethers derived from mustard gas and its analogues. Part I. Possible uses for analysis." By E. M. MEADE and R. C. G. MOGGRIDGE.

" The methyl thioethers derived from mustard gas and its analogues. Part II. Pyrolysis experiments." By R. J. CHARNOCK and R. C. G. MOGGRIDGE.

" The methyl thioethers derived from mustard gas and its analogues. Part III. Synthetic experiments." By R. BROWN and R. C. G. MOGGRIDGE.

" Contribution to the chemistry of pyridine. Condensation of β-hydroxypyridine with formaldehyde in alkaline medium." By T. URBANSKI.

" An improved analysis of fuming and concentrated sulphuric acid by water titration." By J. C. D. BRAND.

" Methylene chloroamine." By (MISS) M. LINDSAY and F. G. SOPER.

" The structure of dimeric keten : Infra-red measurements." By D. H. WHIFFEN and H. W. THOMPSON.

" 4 : 4′-Dinitrodiphenylsulphone." By H. BURTON and W. A. DAVY.

" The synthesis of 3-methyl*iso*quinolines. Part II." By G. R. CLEMO and J. H. TURNBULL.

" The ionisation of acridine bases." By A. ALBERT and R. GOLDACRE.

" Synthetic antimalarials. Part VIII. Some 4-arylamino-6-basicalkylamino-2-methylpyrimidines." By F. R. BASFORD, F. H. S. CURD, and F. L. ROSE.

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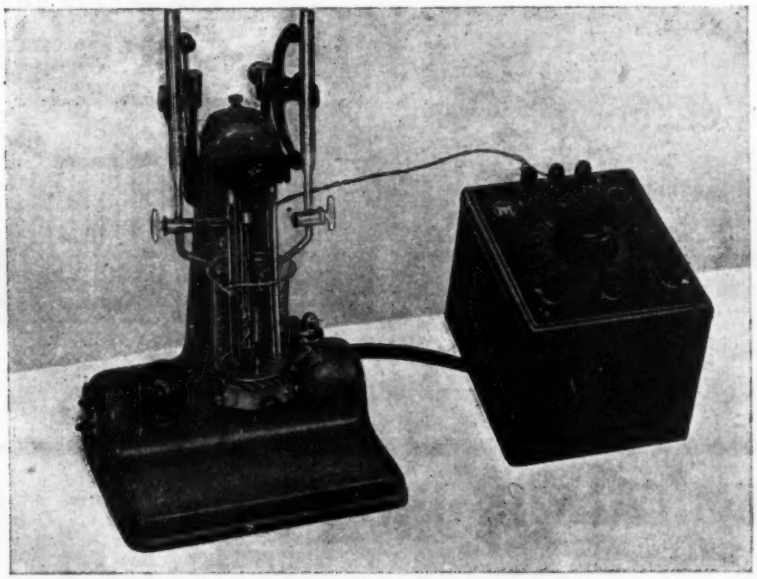

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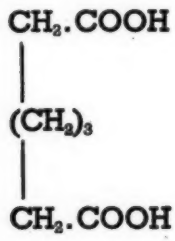

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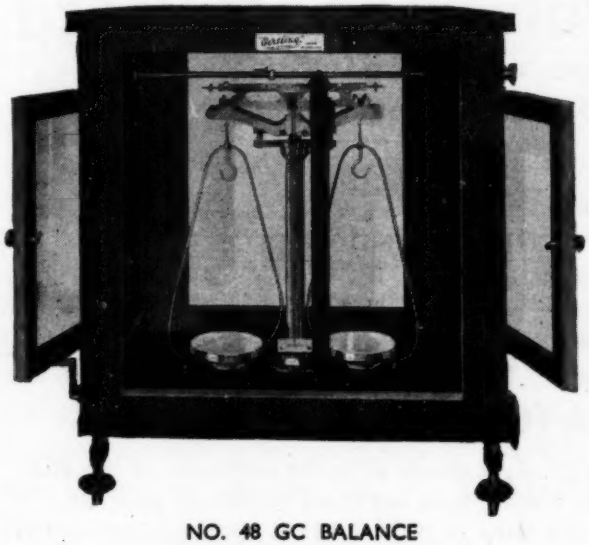

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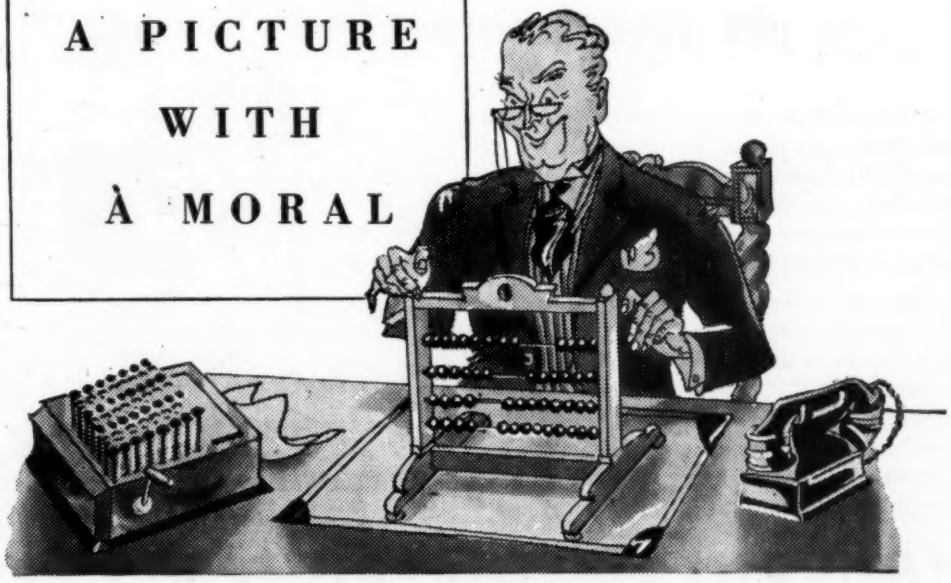

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## 18. *Acid Catalysis in the Formation of Chloroamides from Hypochlorous Acid. N-Chlorination by Hypochlorite Ions and by Acyl Hypochlorites.*

By (Miss) Rhoda P. Mauger and F. G. Soper.

Further evidence is given for the view that the formation of chloroamides from hypochlorous acid involves the hypochlorite ion as chlorinating agent. *N*-Methylacetamide is *N*-chlorinated in this way and in addition is *N*-chlorinated at a rate dependent on the product of the concentrations of hypochlorous acid and of the free acid used as a component of the buffering solution. This is interpreted in terms of the formation of acyl hypochlorites which act as chlorinating agents. With acetanilides, the latter mechanism appears to be absent, and *N*-chlorination by hypochlorous acid is apparently determined solely by the first mechanism. *N*-Chlorination by hypochlorous acid, by chlorine, by another chloroamine, and by acyl hypochlorites are separate and distinct mechanisms.

The rate at which chloroamines are formed from chlorine or from hypochlorous acid can be measured by a method (Orton, Soper, and Williams, J., 1928, 998; Pryde and Soper, J., 1931, 1510) which depends on first removing the free chlorinating agent by a phenol with which the chloroamine does not react appreciably. The chloroamine can then be estimated iodometrically. This method has been found of general applicability. Pryde and Soper studied the formation of *N*-chloroanilides from anilides and hypochlorous acid in buffered solutions and over a range of hydrogen-ion concentration of 0·6—2·6 $\times$ $10^{-6}$ found that the rate of formation was proportional to the hydroxyl-ion concentration. This result was interpreted as indicating that *N*-chlorination by hypochlorous acid occurred *via* the hypochlorite ion. It seemed desirable to examine this conclusion further by studying *N*-chlorination in pH regions where the hypochlorite-ion concentration expressed as a fraction of the total concentration of hypochlorous acid and hypochlorite would not be simply proportional to the hydroxyl-ion concentration. The fraction of the total concentration of hypochlorous acid plus hypochlorite which is present as hypochlorite varies with pH as set out in Table I. These figures are based on the value of the ionisation constant of hypochlorous acid obtained by Ingham and Morrison (J., 1933, 1200), *viz.*, 3·47 $\times$ $10^{-8}$ at 18°. From the heat absorbed on ionisation of the acid, *i.e.*, 3,970 cals. (I.C.T., Vol. V, p. 176), the value of the constant at 25° may be calculated as 4·1 $\times$ $10^{-8}$. Hence, if *N*-chlorination by hypochlorous acid is dependent on the hypochlorite-ion concentration, the specific rate, $k_2$, defined by $v = k_2$[HOCl + OCl′][:NH], should increase with alkalinity as set out below, increasing 8-fold from pH 6·0 to 7·0 and 2·8 times from pH 7·0 to 8·0.

Table I.

| pH | 5·0 | 6·0 | 7·0 | 8·0 | 9·0 |
|---|---|---|---|---|---|
| Percentage of [HOCl + OCl′] as [OCl′] | 0·408 | 3·94 | 29·1 | 80·4 | 97·6 |

It was found that *N*-methylacetamide formed a stable chloroamine over the range of pH 3—9 and was therefore suitable for examination. It was not possible to examine satisfactorily the rate of formation of chloroamine from acetamide, owing to the instability of the former. Although *N*-chloroacetamide when pure is reasonably stable in aqueous solution, it becomes very unstable in the presence of hypochlorous acid, owing presumably to the formation of unstable dichloroamine (see Experimental section). A preliminary examination of the results obtained by using *N*-methylacetamide and phosphate buffers (pH 6—8) showed that the rate increased with pH, but at pH 5·0 in presence of an acetate buffer, the rate, instead of being less, was 10 times as great as at pH 6·0 in presence of a phosphate buffer. Velocity coefficients at pH 5·0 and pH 6·0, calculated from the equation $v = k_2$[HOCl + OCl′][amide] for a series of acetate buffers from half to twice the usual concentrations of acid and salt (Walpole, J., 1914, **105**, 2501), are given in Table II.

Table II.

| Fraction of usual buffer concn. | 2. | 1·67. | 1·33. | 1. | 0·67. | | 0·25. |
|---|---|---|---|---|---|---|---|
| | | | pH = 6·0. | | | | |
| NaOAc | 6·3850 | 0·3208 | 0·2567 | 0·1925 | 0·1283 | 0·09625 | — |
| HOAc | 0·0150 | 0·0125 | 0·0100 | 0·0075 | 0·0050 | 0·00375 | — |
| $k_2$ | 0·501 | 0·432 | 0·351 | 0·301 | 0·224 | 0·193 | — |
| | $k_0$ (= $k_2$ extrapolated to zero concentration of buffer) = 0·085. | | | | | | |
| | | | pH = 5·0; $k_0$ 0·05. | | | | |
| NaOAc | 0·280 | 0·233 | 0·187 | 0·14 | 0·0933 | — | 0·0350 |
| HOAc | 0·120 | 0·100 | 0·080 | 0·060 | 0·040 | — | 0·0150 |
| $k_2$ | 3·381 | 2·779 | 2·145 | 1·640 | 1·154 | — | 0·472 |

The variation in $k_2$ with strength of the buffer solution was shown not to be due to an ionic-strength effect, for additions of potassium nitrate up to 0·6M had but slight effect on the specific rate. Variation of sodium acetate concentration from 0·035 to 0·385M at constant acetic acid concentration (0·015M) changed $k_2$ from 0·472 to 0·501. This alteration in sodium acetate concentration corresponded to a change in pH from 5·0 to 6·0 and showed that pH was of minor effect on the specific rate. A corresponding series of experiments at constant sodium acetate concentrations of 0·0933M and acetic acid concentrations of 0·04M and 0·00375M (pH 5·0 and 6·0, respectively) changed $k_2$ from 1·154 to 0·193, which indicated that the accelerating effect observed on increasing the concentration of the buffer was due in the main to the change in the concentration

of acetic acid. The increase in $k_2$ due to an increase in concentration of acetic acid of 0·1M, calculated from a series of experiments at pH 5·0, was found to be 2·78, and from a series at pH 6·0 was 2·77. The accelerating effect of free acetic acid on the rate of *N*-chlorination is thus the same at pH 5·0 as at pH 6·0.

Curves obtained at pH's 3·0—6·0 by plotting $k_2$ against acid concentration, various weak acids being used as components of the buffering mixtures, are shown in Fig. 1. In these acid solutions where the concentration of hypochlorite ions is small the speed appears to be satisfactorily given by the equation $v = k_A[HA][HOCl][{:}NH]$, *i.e.*, the bimolecular constant $k_2$ as already defined $= k_A[HA]$, and $k_A$ is given by the slope of the lines in Fig. 1. The catalytic coefficients obtained in this way are given in Table III. The ionisation constants utilised are those obtained respectively by Cohn, Heyroth, and Menkin (*J. Amer. Chem. Soc.*, 1928, **50**, 696),

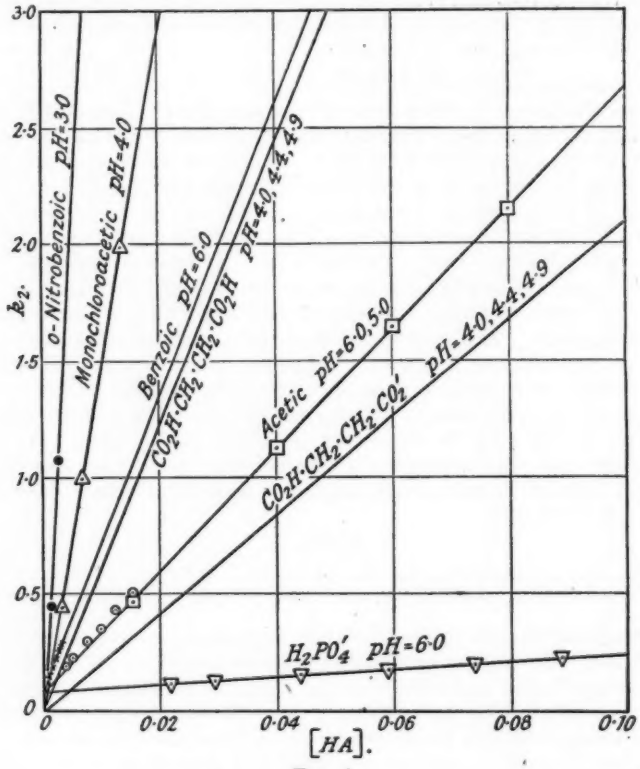



FIG. 1.

TABLE III.

| Acid. | Acetic. | Benzoic. | Monochloroacetic. | *o*-Nitrobenzoic. | Succinic. (1). | Succinic. (2). |
|---|---|---|---|---|---|---|
| $k_A$ ..... | 27 | 62 | 150 | 440 | 61 | 21 |
| $K_a \times 10^5$ ..... | 1·86 | 6·37 | 155 | 671 | 6·89 | 0·247 |

Vogel and Jeffrey (*Chem. and Ind.*, 1934, 779), Ostwald (*Z. physikal. Chem.*, 1889, **3**, 176), Dippy and Lewis (J., 1937, 1426), and Jones and Soper (J., 1936, 133). The values for $k_A$ for succinic acid were obtained from experiments in succinate buffers at pH's 4·0, 4·4, and 4·9, which allowed of determination of the separate coefficients for the un-ionised acid and for the acid succinate anion. The relation of the catalytic coefficients, $k_A$, to the ionisation constant of the acid is shown in Fig. 2.

Owing to the smallness of $k_0$ (obtained by extrapolation) in acid solutions, a series of measurements of the rate of *N*-chlorination was made in phosphate buffers from pH 6—9. The results are given in Table IV.

TABLE IV.

*N-Chlorination of N-methylacetamide.*

| | pH 6; $k_0$ (by extrapolation) = 0·07. | | | | pH 7; $k_0$ = 0·31. | | | |
|---|---|---|---|---|---|---|---|---|
| $H_2PO_4'$ ..... | 0·08860 | 0·06645 | 0·04430 | 0·02215 | 0·04074 | 0·03055 | 0·02037 | 0·01018 |
| $HPO_4''$ ..... | 0·01140 | 0·00855 | 0·00570 | 0·00285 | 0·05926 | 0·04445 | 0·02963 | 0·01482 |
| $k_2$ ..... | 0·231 | 0·190 | 0·152 | 0·111 | 0·382 | 0·366 | 0·343 | 0·330 |
| | pH 8·0; $k_0$ = 0·72. | | | | pH 9·0; $k_0$ (estimated) = 0·90. | | | |
| $H_2PO_4'$ ..... | 0·00640 | 0·00480 | 0·00320 | 0·00161 | | — | | |
| $HPO_4''$ ..... | 0·09360 | 0·07020 | 0·04680 | 0·02340 | | 0·100 | | |
| $k_2$ ..... | 0·774 | 0·773 | 0·738 | 0·736 | | 0·958 | | |

The increase in the value of $k_0$ defined by the equation $v = k_0[HOCl + OCl'][:NH]$ obtained by extrapolation to zero acid concentration is closely paralleled by the increasing ionisation of hypochlorous acid. If in the absence of acids the speed is determined by $v = k_{OCl'}[OCl'][:NH]$, then $k_{OCl'} = k_0[HOCl + OCl']/[OCl']$. These values of $k_{OCl'}$ are given below, and correspond to an increase in the fraction $[OCl']/[HOCl + OCl']$ from 3·9% at pH 6·0 to 97·6% at pH 9·0.

| pH | 6·0 | 7·0 | 8·0 | 9·0 |
|---|---|---|---|---|
| $k_0$, mol.$^{-1}$ min.$^{-1}$ | 0·07 | 0·31 | 0·72 | 0·90 |
| $k_{OCl'}$, mol.$^{-1}$ min.$^{-1}$ | 1·78 | 1·075 | 0·895 | 0·922 |

*N-Chlorination of Acetanilide.*—In view of the effects observed with *N*-methylacetamide, acetanilide was re-examined in a series of phosphate buffers. Unlike that of *N*-methylacetamide, the rate of *N*-chlorination of acetanilide was not increased by increase of buffer concentration. The specific rate, $k_2$, in the case of *N*-methylacetamide is increased at pH 6·0 from 0·152 to 0·231 on doubling the usual concentration of the phosphate buffer (Clark and Lubs, *J. Biol. Chem.*, 1916, **25**, 479); the corresponding figures for acetanilide show a decrease from 13·2 to 11·3 (cf. Pryde and Soper, *loc. cit.*, 10·3). Similar experiments on acetanilide in acetate buffers at pH 6·0 gave values for $k_2$ of 13·7 and 14·1, of similar magnitude to those observed in phosphate at pH 6. In the case of *N*-methylacetamide the change at pH 6·0 from phosphate buffer to acetate buffer increased $k_2$ by 98%, *i.e.*, from 0·152 to 0·301, the latter value rising by a further 66% to 0·501 on doubling the concentration of the acetate buffer.

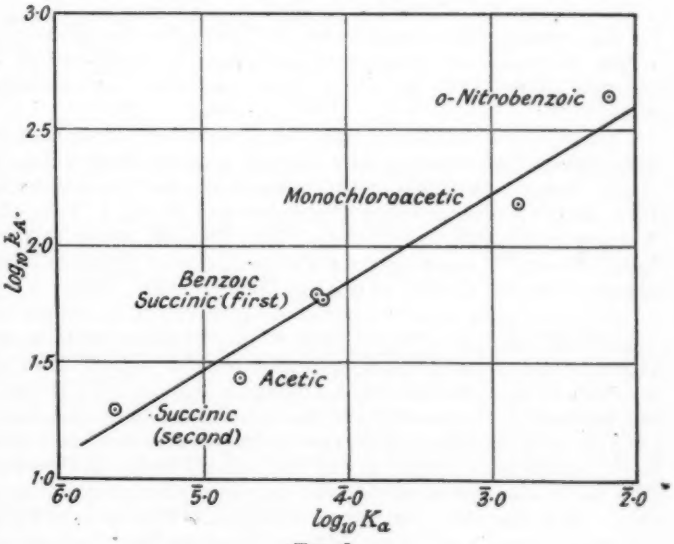



FIG. 2.

It appears therefore that the *N*-chlorination of acetanilide (and other anilides—see Experimental section) by hypochlorous acid is not appreciably catalysed by acids. The values for $k_2$ observed for acetanilide show a similarity to the coefficients $k_0$ for *N*-methylacetamide in that they increase with increasing ionisation of the hypochlorous acid. Values of $k_2$ at pH 5·0—8·0 and of $k_{OCl'}$, defined by $v = k_{OCl'}[OCl'][:NH]$, are given below.

*N-Chlorination of acetanilide.*

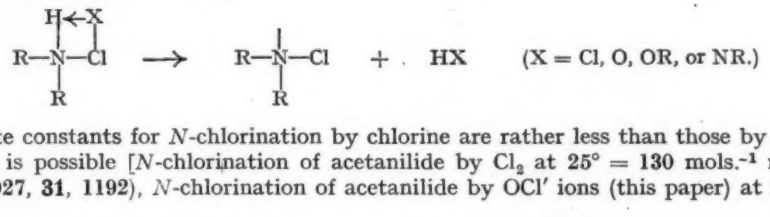
| pH | 5·0 | 6·0 | 7·0 | 8·0 |
|---|---|---|---|---|
| $k_2$, mol.$^{-1}$ min.$^{-1}$ | 1·37 | 13·2 | 99 | 269 |
| $k_{OCl'}$, mol.$^{-1}$ min.$^{-1}$ | 335·5 | 335·1 | 340·4 | 342·5 * |

* If the thermodynamic ionisation constant of hypochlorous acid is used (Ingham and Morrison, *loc. cit.*), *viz.*, $2{\cdot}95 \times 10^{-8}$ at 18°, and a calculated value at 25° of $3{\cdot}47 \times 10^{-8}$, the corresponding values of $k_{OCl'}$ are 395, 393, 384, and 347.

Thus the *N*-chlorination of acetanilide by hypochlorous acid is satisfactorily explained by interaction of the anilide and hypochlorite ions and apparently there is inappreciable *N*-chlorination by hypochlorous acid molecules. This mechanism applies also to *N*-methylacetamide in low concentrations of acid, but in higher concentrations of acids the chlorination is mainly dependent on the product of the concentrations of the amide, acid, and hypochlorous acid.

In view of the fact that *N* : 2 : 4 : 6-tetrabromoacetanilide brominates anisole in the presence of an acid such as acetic but not in its absence, Israel, Tuck, and Soper suggested (J., 1945, 547) that an intermediate brominating agent, bromine acetate, was formed from the *N*-bromo-compound and acetic acid. In the formation of *N*-chloromethylacetamide, a similar catalysing effect of acids has been observed and an explanation of the present results is that the acid and hypochlorous acid form a compound analogous to the bromine acetate previously postulated, *i.e.*, a chlorine acetate or, in general, an acyl hypochlorite, $R{\cdot}CO_2H + HOCl \rightleftharpoons R{\cdot}CO{\cdot}OCl + H_2O$, which is presumed to be a highly efficient chlorinating agent. Evidence for acyl halogenites has been obtained by Bockemüller and Hoffmann (*Annalen*, 1935, **519**, 165), who prepared them in nitrobenzene and in carbon tetrachloride solution by interaction of halogen and silver salts. The effect of increasng concentrations of acid in the present work is to increase proportionally the concentration of the acyl hypochlorite. The fact that *N*-methylacetamide and acetanilide behave differently towards this agent is of interest. Other anilides, *e. g.*, *o*-chloracetanilide, *o*- and *p*-acetotoluidide, behave similarly to acetanilide in showing no appreciable chlorination by acyl hypochlorite, whereas acetylglycine resembles *N*-methylacetamide in showing an accelerating effect of acids on the *N*-chlorination at constant pH, indicating chlorination by acyl hypochlorite.

*N*-Chlorination may occur by various chlorinating mechanisms of which the following have been studied kinetically: (*a*) the action of molecular chlorine (Orton, Soper, and Williams, *loc. cit.*), (*b*) the action of hypochlorite ions (Pryde and Soper, *loc. cit.*; and this paper), (*c*) the action of another chloroamine (*N*-chloroacetanilide reacts directly with *p*-toluenesulphonamide, Pryde and Soper, J., 1931, 1514), and (*d*) by the action of acyl hypochlorites (this paper). In all cases the *N*-chlorination may be envisaged as depending on preliminary hydrogen bond formation between the amino-hydrogen and an oxygen, nitrogen, or chlorine atom (in the chlorinating molecule) acting as donor atom:




The specific rate constants for *N*-chlorination by chlorine are rather less than those by hypochlorite ions where comparison is possible [*N*-chlorination of acetanilide by $Cl_2$ at 25° = 130 mols.$^{-1}$ mins.$^{-1}$ (Soper, *J. Physical Chem.*, 1927, **31**, 1192), *N*-chlorination of acetanilide by OCl′ ions (this paper) at 25° = 338 mols.$^{-1}$ mins.$^{-1}$].*

The removal of halogen from halogenoamine corresponds to the reverse of the above reactions and halogenoamines react directly with halogen acids to form halogens and mixed halogens (Orton and Jones, *Brit. Assoc. Reports*, 1910, 85), with hydroxyl ions to form hypochlorite ions (unpublished work), with alcohols to form alkyl hypochlorite ions (Chattaway and Orton, J., 1899, **75**, 1047; Likhosherstov and Sklyarov, *Acta Univ. Voronegiensis*, 1935, **8**, 47; *Chem. Abs.*, 1938, **32**, 4524), and with acids other than halogen acids to form acyl hypohalogenites accounting for the general acid catalysis of the isomerisation of the *N*-halogenoacetanilides observed by Bell and his co-workers (Bell, J., 1936, 1154).

*N*-Chlorination as envisaged above involves (*a*) hydrogen bond formation by the amino-hydrogen with the oxygen, nitrogen, or chlorine atom of the halogenating molecule and (*b*) electron release by the chlorine atom of the halogenating molecule, whereby the chlorine atom becomes a positive chlorine ion. The other stages, *viz.*, the chlorine attachment and proton release by the nitrogen atom are constant factors in the *N*-chlorination of a particular substance.† The greater efficiency in *N*-chlorination of the OCl′ ion in comparison with molecular chlorine is understandable in view of the greater tendency of the oxygen in the OCl′ ion to form a hydrogen bond, which is envisaged as the preliminary step. No evidence was obtained for *N*-chlorination by HOCl. This fact is due presumably to the decreased electron-donating power of the oxygen in HOCl as compared with OCl′. It is therefore difficult to understand why an acyl hypochlorite should be such an active chlorinating agent for certain substances such as *N*-methylacetamide and acetylglycine.

In the acyl hypochlorite the donor properties of the hypochlorite oxygen should be less than in hypochlorous acid (relative inductive effects of O–H and O–C), and its tendency to form hydrogen bonds and cause *N*-chlorination should likewise be less. In view of the fact that the acyl hypochlorite is not apparently an active *N*-chlorinating agent for the anilides, the explanation of its activity in chlorinating *N*-methylacetamide may be due to some constitutional property of the latter. Thus the *iso*amide structure has been advocated for trichloroacetamide (Hantzsch, *Ber.*, 1931, **64**, 661) on the basis of a comparison of its absorption spectrum with those of its *O*- and *N*-derivatives. If *N*-methylacetamide is partly in the *iso*amide form, $CH_3 \cdot N{:}C(OH) \cdot CH_3$, the acyl hypochlorite may add on across the double bond (Bockemüller and Hoffmann, *loc. cit.*) in a manner analogous also to the way in which phenyl hypochlorite, PhOCl, adds on to butylene to give 2-chloro-3-phenoxybutane (Likhosherstov and Arkhangel'skaya, *J. Gen. Chem. U.S.S.R.*, 1937, **7**, 1914). Such an explanation would require that the aliphatic amides exist to a much greater extent in the *iso*amide structure than do the anilides; otherwise, the anilides also should be *N*-chlorinated by acyl hypochlorites. The evidence from ultra-violet absorption spectra for the *iso*amide structure of anilides, based on the dissimilarity of the absorption curves of *N*-methylacetanilide and acetanilide (Ramart-Lucas and Wohl, *Compt. rend.*, 1933, **196**, 120), is slight, for in the anilides substitution of the amino-hydrogen by methyl would tend to reduce the resonance of the $\cdot NH \cdot CO \cdot$ system which, in the contributing form $\cdot \overset{+}{N}H{:}\overset{-}{C}O \cdot$, is conjugated with the benzene ring and hence might be expected to affect considerably the absorption, independently of any effect due to the possible structure, $\cdot N{:}C(OH) \cdot$. The difference in the absorption spectra of acetanilide and *N*-methylacetanilide cannot therefore be regarded as evidence for the *iso*amide structure of the former.

## Experimental.

*Hypochlorous Acid.*—Hypochlorous acid (Pryde and Soper, *loc. cit.*) was stored over mercuric oxide, and before use was shaken with fresh yellow mercuric oxide and centrifuged.

*N-Methylacetamide.*—A cold solution of freshly distilled acetic anhydride in 3 vols. of dry ether was added slowly to excess of methylamine in dry ether. The reaction mixture was kept below − 10° for an hour. The product was purified by stirring with a little water and potassium carbonate until alkaline to litmus, and the ether portion was then

* The figures for $k_{OCl'}$ ($k_N$, Pryde and Soper, *loc. cit.*) were calculated on a limited range of pH using a value for $K_a^{HOCl}$ of $1{\cdot}0 \times 10^{-8}$ and are therefore some 3 times too large.

† *C*-Chlorination shows marked contrasts with *N*-chlorination in that $Cl_2$ is greatly more efficient than HOCl in the chlorination of phenols, and in the *C*-chlorination of anilides there is no evidence that the OCl′ ion can cause nuclear chlorination at all.

dried with anhydrous potassium carbonate and fractionated, the main portion distilling at 120—125° (column temp.)/40 mm. and solidifying to very hygroscopic colourless needles, m. p. 27·8° (cf. 28°; Hofmann, *Ber.*, 1881, **14**, 2729).

*Buffer Solutions.*—For succinic, benzoic, *o*-nitrobenzoic, and monochloroacetic acids, the buffers were prepared so as to give the desired pH (± 0·01 unit) against a Cambridge glass-electrode pH meter standardised with 0·05M-potassium hydrogen phthalate. The stability of hypochlorous acid to the buffer was tested for each experiment.

*Velocity Measurement.*—Hypochlorous acid and amide solutions of twice the required strength were prepared in buffers. When both solutions had attained the temperature of the thermostat, 25·0° (± 0·02°), the reaction was started by addition of 50 c.c. of the hypochlorous acid solution to an equal volume of the amide solution.

The composition of the reaction mixture was then determined at suitable intervals by transferring 5-c.c. portions to (*a*) 5 c.c. of 3% freshly distilled phenol, shaking for 10 seconds, followed by the addition of 5 c.c. of 5N-acetic acid then 5 c.c. of 2% potassium iodide, whereby the chloroamide titre was determined, and (*b*) 5 c.c. of 5N-acetic acid followed by 5 c.c. of 2% potassium iodide, which gives the hypochlorous acid + chloroamide titre, the iodine liberated being titrated against N/200- or N/500-thiosulphate.

The results for a typical experiment are given below.

$CH_3{\cdot}CO_2H$ = 0·0150M; $CH_3{\cdot}CO_2Na$ = 0·385M; $CH_3{\cdot}CO{\cdot}NH{\cdot}CH_3$ = 0·0200M; HOCl = 0·00457M.

| Time (mins.) | 1·00 | 10·00 | 14·25 | 30·0 | 50·0 | 70·0 | 90·0 | 93·5 | 120·0 |
|---|---|---|---|---|---|---|---|---|---|
| Titre of :NCl, c.c. | 0·17 | 0·94 | — | 2·41 | 3·56 | 4·52 | 5·24 | — | 6·15 |
| Total titre, c.c. | — | — | 9·25 | — | — | — | — | 9·20 | — |
| $k_2$ | — | 0·499 | — | 0·505 | 0·502 | 0·505 | 0·497 | — | 0·497 |

$k_2$ = 0·501 ± 1%.

In the case of acetamide, the chloroamide formed was unstable in the presence of hypochlorous acid. The stability of this chloroamide to hypochlorous acid in phosphate buffer pH 7·0 is given below.

$KH_2PO_4$ = 0·050M; NaOH = 0·0296M; $CH_3{\cdot}CO{\cdot}NHCl$ = 0·020M; HOCl = 0·010M. Temp. = 13°.

| Time (mins.) | 1·00 | 2·00 | 20·00 | 28·50 | 75·00 | 85·00 | 182·5 | 184·0 | 1080 |
|---|---|---|---|---|---|---|---|---|---|
| Titre of :NCl, c.c. | — | 38·28 | — | 34·05 | 27·24 | — | 19·21 | — | 10·25 |
| Total titre, c.c. | 53·62 | — | 43·90 | — | — | 29·75 | — | 21·12 | 10·56 |

*N*-Chloroacetamide in the absence of hypochlorous acid shows only slight decomposition under similar conditions.

*Catalytic Effects of Acids.*—The values of $k_2$ plotted against the concentration of acid are shown in Fig. 1, and the catalytic coefficients recorded in Table III. For succinic acid buffers, where catalysis is due both to the acid and the acid anion, $k_2 = k_{H_2A}[H_2A] + k_{HA'}[HA']$, a series of measurements using different amounts of the buffer mixture were made at pH's 3·96, 4·43, and 4·94; $k_2$ increased linearly with increase of buffer concentration. Substitution for the acid and acid anion concentrations at two different pH values allows of solution of the separate catalytic coefficients $k_{H_2A}$ and $k_{HA'}$. The calculated and observed values for $k_2$, values of $k_{H_2A}$ and $k_{HA'}$ of 61 and 21 being used, obtained as indicated, are given below.

*Catalytic influence of succinate buffers.*

$CH_3{\cdot}CO{\cdot}NHCH_3$ = 0·0200M; HOCl = 0·0050M; temp. = 25·0° (± 0·02°).

| pH. | $[H_2A]$. | $[Na_2A]$. | $[H_2A]$, calc. | $[HA']$, calc. | $k_2$. | $k$, calc. |
|---|---|---|---|---|---|---|
| 3·96 | 0·1398 | 0·03612 | 0·1662 | 0·0104 | 9·99 | 10·36 |
| | 0·1049 | 0·02709 | 0·1247 | 0·0078 | 6·95 | 7·77 |
| | 0·0699 | 0·01806 | 0·0831 | 0·0052 | 5·03 | 5·18 |
| | 0·0350 | 0·00903 | 0·0416 | 0·0026 | 2·36 | 2·59 |
| 4·43 | 0·06085 | 0·03915 | 0·0337 | 0·0623 | 3·41 | 3·37 |
| | 0·03043 | 0·01958 | 0·0169 | 0·0312 | 1·81 | 1·69 |
| | 0·01521 | 0·00979 | 0·0084 | 0·0156 | 1·0 | 0·84 |
| 4·94 | 0·05209 | 0·06875 | 0·01460 | 0·0875 | 2·57 | 2·73 |
| | 0·04167 | 0·05500 | 0·01168 | 0·0700 | 2·08 | 2·18 |
| | 0·02084 | 0·02750 | 0·00584 | 0·0350 | 1·08 | 1·09 |
| | 0·01042 | 0·01375 | 0·00292 | 0·0175 | 0·558 | 0·55 |

*Absence of Acid Catalysis in the N-Chlorination of Anilides.*—Values of $k_2$ observed in phosphate and acetate buffers are shown below. The velocity coefficients refer to the following substances: (1) *o*-chloroacetanilide, (2) *o*-acetotoluidide,

*Velocity coefficients of N-chlorination.*

| Buffer pH. | Molar concn. of buffer acid. $CH_3{\cdot}CO_2H$. | Molar concn. of buffer salt. $CH_3{\cdot}CO_2Na$. | (1). | (2). | (3). | (4). | (5). | (6). |
|---|---|---|---|---|---|---|---|---|
| Acetate, 6·0 ..... | 0·00375 | 0·0963 | 155 | 13·0 | — | — | 0·356 | 0·193 |
| ,, ..... | 0·00750 | 0·1925 | 149 | 12·5 | 13·7 | 10·8 | 0·387 | 0·301 |
| ,, ..... | 0·0150 | 0·3850 | 148 | — | 14·1 | 11·0 | 0·462 | 0·501 |
| | $H_2PO_4'$. | $HPO_4''$. | | | | | | |
| Phosphate, 6·0 ... | 0·0443 | 0·00574 | 145 | — | 13·2 | 10·8 | 0·280 | 0·152 |

(3) acetanilide, (4) *p*-acetotoluidide (5), acetylglycine, (6) *N*-methylacetamide. No acid catalysis is observed for substances (1)—(4), and the velocity coefficients observed in phosphate buffers are similar to those in acetate buffers.

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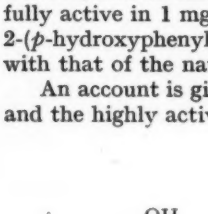
## 19. *New Naphthalene Derivatives Structurally Related to Stilboestrol.*

By B. J. F. Hudson.

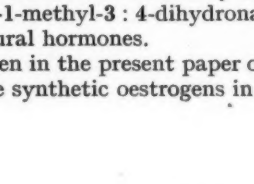
A series of *p*-methoxyphenyl 2-methoxynaphthyl ketones are obtained by the use of Friedel–Crafts condensations. Subsequent reduction and demethylation afford dihydroxy compounds spatially related to stilboestrol. Using rats, oestrogenic activity in the compounds tested was shown to be less than one-thousandth of that of stilboestrol.

Naphthalene derivatives do not appear to have been investigated hitherto as possible oestrogenic agents, although a tetrahydronaphthalene and a hexahydrochrysene derivative were investigated by Dodds, Golberg, Lawson, and Robinson (*Proc. Roy. Soc.*, B, 1941, **127**, 140). The former had slight activity, but the latter was fully active in 1 mg. doses. More recently Salzer (*Z. Physiol. Chem.*, 1942, **274**, 39) has prepared 6-hydroxy-2-(*p*-hydroxyphenyl)-1-methyl-3 : 4-dihydronaphthalene, which is stated to exhibit an activity comparable with that of the natural hormones.

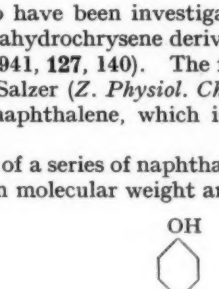
An account is given in the present paper of a series of naphthalene derivatives closely resembling oestradiol and the highly active synthetic oestrogens in molecular weight and spatial configuration.



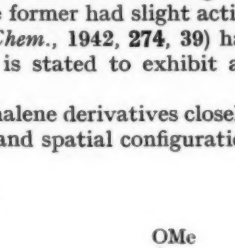
(I.)



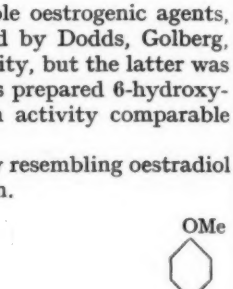
(II.)



(III.)



(IV.)



(V.)

Compounds of type (I) have now been obtained from 2-*methoxy*-6-*anisoylnaphthalene* which is derived from 2-methoxy-6-naphthoic acid by the condensation of anisole with 2-methoxy-6-naphthoyl chloride. Reduction of 2-methoxy-6-anisoylnaphthalene by Clemmensen's method yields p-*methoxyphenyl*-(2-*methoxy*-6-*naphthyl*)-*methane*, the dimethyl ether of (I, R = H). On the other hand reaction with methylmagnesium iodide leads directly to α-(p-*methoxyphenyl*)-α-(2-*methoxy*-6-*naphthyl*)-*ethylene* (IV) which on hydrogenation gives the dimethyl ether of (I, R = Me). Dealkylation of this ether gives no well-defined product.

It is well known that, when the solvent is cold nitrobenzene, the course of a Friedel–Crafts reaction with 2-substituted naphthalenes can be modified so that an acyl group enters the 6-position (Haworth and Sheldrick, *J.*, 1934, 865; Anderson and Johnston, *J. Amer. Chem. Soc.*, 1943, **65**, 241). The present work confirms this as far as the action of acyl chlorides on 2-methoxynaphthalene is concerned, but it has also been shown that, even in cold nitrobenzene, as well as in carbon disulphide, the anisoyl group enters the 1-position. An independent synthesis of the product, 2-*methoxy*-1-*anisoylnaphthalene*, has been achieved by the action of anisole on 2-methoxy-1-naphthoyl chloride.

Ketones leading to compounds (II) and (III) were obtained by the action of *p*-methoxyphenylacetyl chloride and β-*p*-methoxyphenylpropionyl chloride respectively on 2-methoxynaphthalene in the presence of aluminium chloride and nitrobenzene. Their structures were established by the oxidation of the reaction products to 2-methoxy-6-naphthoic acid. Reduction followed by demethylation gave (II) and (III).

A second approach to (III) has been made by condensing 2-*methoxy*-6-*naphthaldehyde*, obtained from 2-methoxy-6-naphthylmagnesium bromide by the action of ethyl orthoformate, with *p*-methoxyacetophenone, followed by hydrogenation of the resulting chalkone to the ketone (V).

Biological assay of compounds (I, R = H), (II), (III) and their diacetates was carried out by Dr. G. Brownlee of the Wellcome Physiological Research Laboratories, Beckenham. They were shown by both the uterine weight and vaginal smear methods, using rats, to have less than one-thousandth of the activity of stilboestrol.

### Experimental.

(Melting points are uncorrected.)

2-*Methoxy*-6-*anisoylnaphthalene*.—2-Methoxy-6-naphthoic acid (Fries and Schimmelschmidt, *Ber.*, 1925, **58**, 2840) (33·2 g.) was refluxed with excess of thionyl chloride for one hour, excess of thionyl chloride evaporated, and the resulting crystalline acid chloride gradually added to a cold stirred mixture of anisole (38 g.), dry carbon disulphide (200 c.c.), and freshly powdered aluminium chloride (52·5 g.). The deep orange-red solution was gradually heated to boiling during two hours, cooled, poured on ice, and then steam-distilled. The crude non-volatile product was recrystallised from benzene, and gave thin prisms (40 g., 91%), m. p. 146—147° (Found: C, 77·9; H, 5·6. $C_{19}H_{16}O_3$ requires C, 78·1; H, 5·5%). It formed a scarlet 2 : 4-dinitrophenylhydrazone.

2-*Methoxy*-1-*anisoylnaphthalene*.—(*a*) 2-Methoxy-1-naphthoic acid (14·5 g.) was converted into its acid chloride in the manner described above, and the latter gradually added to a cold stirred mixture of anisole (16·2 g.), carbon disulphide (80 c.c.), and aluminium chloride (22·5 g.). The product, after removal of volatile components by steam-distillation, was a brown gum which on treatment with methanol gave a solid, m. p. 154—158°. This on crystallisation from benzene gave the required product (8·0 g., 48%) in large prisms, m. p. 159—160° (Found: C, 78·2; H, 5·7. $C_{19}H_{16}O_3$ requires C, 78·1; H, 5·5%). A 2 : 4-dinitrophenylhydrazone was not formed under the usual conditions.

(*b*) Anisoyl chloride (11·5 g.) was added to a mixture of 2-methoxynaphthalene (15·8 g.), dry carbon disulphide (100 c.c.), and powdered aluminium chloride (13·5 g.). The reaction and the isolation of the product were carried out as described above; the non-volatile product (9·2 g., 40%) crystallised from benzene in large prisms, m p. 159—160°, identical with the product of (*a*).

(*c*) Anisoyl chloride (17·05 g.) was added slowly to a stirred solution of 2-methoxynaphthalene (15·8 g.) and aluminium chloride (27 g.) in dry nitrobenzene (75 c.c.) at 0°. The orange-red solution was stirred for 7 hours, decomposed by pouring on ice, and steam-distilled. The product was a thick brown oil which, after trituration with methanol, gave a solid (8·1 g., 28%), crystallising from benzene (charcoal) in stout prisms, m. p. 159—160°, identical with the products of (*a*) and (*b*).

p-*Methoxyphenyl*-(2-*methoxy*-6-*naphthyl*)-*methane*.—2-Methoxy-6-anisoylnaphthalene (12·0 g.), amalgamated zinc (150 g.), anisole (40 c.c.), and a mixture of concentrated hydrochloric acid (48 c.c.) and water (24 c.c.) were heated under reflux at 140—150° for 24 hours. The anisole layer was separated, washed with water and dilute sodium hydroxide, and evaporated under reduced pressure. The residual gum could not be crystallised. On distillation, it gave fractions boiling at 260—280°/6 mm. (colourless) and 280—300° (yellow) (3·6 g. in all). The residual resinous material was not volatile. On crystallisation from methanol, the first fraction gave 1·25 g., and the second 0·45 g., m. p. 100—101°. Repeated crystallisation from methanol gave 1·6 g. (14%) of thin prisms, m. p. 103—104° (Found: C, 81·75; H, 6·6. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%).

p-*Hydroxyphenyl*-(2-*hydroxy*-6-*naphthyl*)-*methane* (I, R = H). The above dimethyl ether (2·0 g.) was heated under reflux with acetic acid (16 c.c.) and hydriodic acid (*d* 1·7, 8 c.c.) for one hour, poured into ice-water, decolourised with a trace of sodium bisulphite, collected, washed, and dried to a pink solid. After two crystallisations from benzene, the *product* (1·3 g., 70%), m. p. 159—160°, was obtained (Found: C, 81·0; H, 5·6. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·65%). The *diacetate*, obtained by treatment with acetic anhydride and pyridine, formed thin prisms, m. p. 89—90°, on crystallisation from methanol (Found: C, 75·4; H, 5·5. $C_{21}H_{18}O_4$ requires C, 75·4; H, 5·4%).

α-(p-*Methoxyphenyl*)-α-(2-*methoxy*-6-*naphthyl*)-*ethylene* (IV).—To the Grignard reagent prepared from magnesium (0·66 g.) and methyl iodide (4·7 g.) in ether was added a warm solution of 2-methoxy-6-anisoyl-naphthalene (5·9 g.) in dry benzene (50 c.c.). The mixture was boiled vigorously under reflux for 6 hours, decomposed with ice, and acidified. The benzene–ether layer was separated and the solvents evaporated. The residual coarsely crystalline solid had m. p. 121—123°. After two crystallisations from ethanol or ethyl acetate, the *product* (4·4 g., 75%) was obtained in waxy leaflets, m. p. 124—125° (Found: C, 82·8; H, 6·6. $C_{20}H_{18}O_2$ requires C, 82·7; H, 6·25%).

α-(p-*Methoxyphenyl*)-α-(2-*methoxy*-6-*naphthyl*)-*ethane*.—The above compound (5·0 g.) was hydrogenated at room temperature and 1400 mm. in the presence of dioxan (60 c.c.) and palladised charcoal (3·0 g.). Absorption of hydrogen was complete in two hours. The solution was filtered, the catalyst washed with dioxan, and the filtrate and washings evaporated under reduced pressure. The residual white solid, on recrystallisation from ethanol, gave the product (4·4 g., 88%), m. p. 107—109°. The pure material crystallised from ethanol in clusters of needles, m. p. 109—110° (Found: C, 82·2; H, 7·2. $C_{20}H_{20}O_2$ requires C, 82·2; H, 6·9%).

*Attempted demethylation of the above dimethyl ether.* The following methods were employed, but in all a gummy phenolic product was formed: (*a*) refluxing with acetic acid and hydriodic acid (*d* 1·7) as already described, (*b*) heating with a slight excess of methylmagnesium iodide at 160—170°, (*c*) heating with a solution of potassium hydroxide in ethylene glycol at 225—235°. The oily products could not be obtained solid. The oily acetate, obtained by the action of acetic anhydride and pyridine, distilled over a considerable temperature range (180—250°/2 mm.) showing that the product was not homogenous. No solid diacetate could be isolated.

6-*Bromo*-2-*ethoxynaphthalene*.—In Fries and Schimmelschmidt's (*loc. cit.*) preparation of 6-bromo-2-methoxynaphthalene, the intermediate 1 : 6-dibromo-2-naphthol was converted into 6-bromo-2-naphthol by the action of granulated tin on a boiling mixture of ethanol and concentrated hydrochloric acid. A considerable non-phenolic fraction was always obtained as a solid at this state. After separating from the alkaline solution of 6-bromo-2-naphthol and washing with water, the product was dried and crystallised from methanol or ethanol, from which it separated in plates, m. p. 81—82° (Found: C, 57·3; H, 4·5. $C_{12}H_{11}OBr$ requires C, 57·4; H, 4·4%).

2-*Ethoxy*-6-*naphthoic Acid*.—6-Bromo-2-ethoxynaphthalene (98 g.) dissolved in warm dry benzene (280 c.c.) was added to a suspension of magnesium (15·0 g.) in ether (280 c.c.) which had been previously activated with a little ethyl bromide. Vigorous boiling was maintained for 20 hours, small amounts of ethyl bromide (18·5 c.c. in all) being added periodically to stimulate the formation of the Grignard reagent. The ether was evaporated and the residual thick brown oil added very slowly to a freezing mixture of ether (150 c.c.) and solid carbon dioxide. After reaching room temperature the mixture was decomposed with ice and hydrochloric acid. The colourless 2-*ethoxy*-6-*naphthoic acid* was collected, washed with ether, and crystallised from ethanol (charcoal). The pure acid (28 g., 33%) consisted of prisms, m. p. 204—205° (to an opaque liquid which cleared at 216°) (Found: C, 72·2; H, 5·5. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%).

6-*Anisoyl*-2-*ethoxynaphthalene*.—The acid (27·4 g.) was converted to 2-ethoxy-6-naphthoyl chloride (crystals from benzene, m. p. 85—86°) in the manner described for 2-methoxy-6-naphthoic acid.

The acid chloride was submitted to the Friedel–Crafts reaction with anisole as described for 2-methoxy-6-naphthoyl chloride. The product (25 g.), after crystallisation from benzene or ethanol, was obtained in prisms, m. p. 128—129° (Found: C, 78·4; H, 5·9. $C_{26}H_{18}O_3$ requires C, 78·4; H, 5·9%).

α-(p-*Methoxyphenyl*)-α-(2-*ethoxy*-6-*naphthyl*)-*ethylene*.—A solution of the foregoing ketone (5·0 g.) in warm benzene (25 c.c.) was added to the Grignard reagent from magnesium (0·40 g.) and methyl iodide (3·5 g.) in ether (30 c.c.). The mixture was boiled for five hours and then worked up as for the 6-methoxy analogue. The product crystallised from ethanol (m. p. 116—118°). Repeated crystallisation from ethanol and ethyl acetate gave cream-coloured waxy plates (3 g.), m. p. 120—122° (Found: C, 82·4; H, 6·8. $C_{21}H_{20}O_2$ requires C, 82·9; H, 6·6%).

α-(p-*Methoxyphenyl*)-α-(2-*ethoxy*-6-*naphthyl*)-*ethane*.—The above compound (10 g.) was hydrogenated in dioxan (100 c.c.) in the presence of palladised charcoal (10·0 g.) at 2 atm. and room temperature. The product was worked up as described for the 2-methoxy analogue. Repeated crystallisation from ethanol and ethyl acetate yielded thin plates (4·8 g., 48%), m. p. 96—97° (Found: C, 82·3; H, 7·4. $C_{21}H_{22}O_2$ requires C, 82·3; H, 7·2%). Attempts to demethylate this ether were no more successful than in the case of the dimethyl compound; only oily phenolic mixtures were obtained.

p-*Methoxybenzyl* 2-*Methoxy*-6-*naphthyl Ketone*.—Freshly powdered aluminium chloride (34·0 g.) was slowly added to a well-stirred ice-cold solution of 2-methoxynaphthalene (20·0 g.) and *p*-methoxyphenylacetyl chloride (24·0 g.) in nitrobenzene (100 c.c.). Stirring at 0° was continued for two hours and the temperature was slowly raised to 30° during the next 4 hours. The mixture was decomposed with ice and nitrobenzene, and unchanged 2-methoxynaphthalene removed by steam-distillation. The residual sticky orange solid was collected, washed with water, and boiled with acetone. On cooling, the white solid was collected, washed with acetone, and dried (15·8 g., m. p. 165—168°). Recrystallisation from benzene gave needles (13·9 g., 36%), m. p. 167—169° (Found: C, 78·5; H, 5·9. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%). This compound formed a scarlet 2 : 4-dinitrophenylhydrazone.

The ketone (3·0 g.) was boiled for 10 hours with N-sodium hypochlorite (160 c.c.). Unchanged starting material was separated and the filtrate, on acidification with dilute hydrochloric acid, gave a white precipitate. This was collected,

washed with water, and dried. It crystallised from ethanol in needles, m. p. 209° (sintering at 195°), which showed no depression in m. p. when mixed with authentic 2-methoxy-6-naphthoic acid.

α-(p-*Methoxyphenyl*)-β-(2-*methoxy*-6-*naphthyl*)-*ethane*.—The above ketone (8·0 g.) was boiled with amalgamated zinc (50 g.), concentrated hydrochloric acid (100 c.c.), and *p*-methylanisole (25 c.c.) for 16 hours at 130—140°. Solvents were removed by steam-distillation and the residual sticky solid separated from unchanged zinc, collected, washed with water and crystallised from ethanol. The separated product (3·5 g.) on crystallisation from ethyl acetate afforded colourless plates (3·15 g., 40%), m. p. 140—141° (Found : C, 81·9; H, 6·85. $C_{20}H_{20}O_2$ requires C, 82·1; H, 6·9%).

α-(p-*Hydroxyphenyl*)-β-(2-*hydroxy*-6-*naphthyl*)-*ethane* (II).—The dimethyl ether (2·0 g.) was refluxed with acetic acid (16·0 c.c.) and hydriodic acid (*d* 1·7, 8·0 c.c.) for 1½ hours, poured into water, and decolourised with sodium bisulphite; the solid was collected, washed and dried. It was twice crystallised from benzene and obtained in prisms (1·1 g., 60%), m. p. 201—202° (Found : C, 81·6; H, 6·15. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%). The *diacetate*, obtained by treatment with acetic anhydride and pyridine, crystallised from methanol in needles, m. p. 138° (Found : C, 75·4; H, 5·65. $C_{22}H_{20}O_4$ requires C, 75·8; H, 5·8%).

β-(p-*Methoxyphenyl*)-*ethyl* 2-*Methoxy*-6-*naphthyl Ketone*.—A Friedel–Crafts reaction was carried out as described for the preparation of *p*-methoxybenzyl 2-methoxy-6-naphthyl ketone using β-(*p*-methoxyphenyl)-propionyl chloride (25·5 g.). The oily product was distilled and the fraction having b. p. 260—290°/2 mm., after repeated crystallisation from methanol gave the required *ketone* (7·4 g., 18%) as prisms, m. p. 100—101° (Found : C, 78·75; H, 6·5. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%). The ketone gave a scarlet 2 : 4-dinitrophenylhydrazone.

This ketone, on oxidation with boiling N-sodium hypochlorite as described above, yielded crude 2-methoxy-6-naphthoic acid, which after crystallisation from ethanol was obtained in needles, m. p. 210°, and there was no depression when mixed with authentic 2-methoxy-6-naphthoic acid.

α-(p-*Methoxyphenyl*)-γ-(2-*methoxy*-6-*naphthyl*)-*propane*.—The ketone (5·0 g.) was refluxed with amalgamated zinc 30 g.), concentrated hydrochloric acid (60 c.c.), and *p*-methylanisole (20 c.c.), at 140° for 16 hours, and worked up in the usual manner. The product (a crude yellow solid) crystallised from ethanol in prisms, m. p. 91—96°. On further crystallisation, first from ligroin (b. p. 60—80°) and then from ethanol, prisms (2·15 g., 45%), m. p. 97—99°, were obtained. They depressed the m. p. of the original ketone (Found : C, 82·05; H, 7·4. $C_{21}H_{22}O_2$ requires C, 82·3; H, 7·2%).

α-(p-*Hydroxyphenyl*)-γ-(2-*hydroxy*-6-*naphthyl*)-*propane* (III).—Demethylation was carried out as described for the homologues, using the dimethyl ether (2·0 g.), glacial acetic acid (12·0 c.c.), and hydriodic acid (*d*, 1·7, 8·0 c.c.). The *product* (0·9 g., 50%) crystallised from benzene in prisms, m. p. 126—128°, which tended to become pink on exposure to air (Found : C, 82·4; H, 7·1. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%). The *diacetate*, prepared by the action of acetic anhydride and pyridine, crystallised from methanol in plates, m. p. 96° (Found : C, 76·2; H, 6·1. $C_{13}H_{22}O_4$ requires C, 76·2; H, 6·1%).

2-*Methoxy*-6-*naphthaldehyde*.—6-Bromo-2-methoxynaphthalene (45 g.) was converted into the Grignard reagent as described by Fries and Schimmelschmidt (*loc. cit.*). After 20 hours' heating, the solution was cooled and stirred and ethyl orthoformate (44 g.) added slowly during one hour, and then boiling was maintained for a further hour. Ether and benzene were evaporated, the thick brown residue heated at 100° for 1½ hours, cooled, decomposed with ice and acetic acid, and extracted with ether. The extract was washed with sodium carbonate solution and water, and the ether evaporated. The residue was shaken for several hours with saturated sodium bisulphite solution, and the solid bisulphite compound collected, washed with ether, and dried. It was then shaken with concentrated hydrochloric acid until decomposition was complete. The aldehyde was collected, washed with water, dried, and crystallised from methanol, giving prisms (6 g., 20%), m. p. 80—81°. This aldehyde yielded a scarlet 2 : 4-dinitrophenylhydrazone and its *semicarbazone* crystallised from acetic acid in leaflets, m. p. 277—280° (becoming yellow at about 250°) (Found : N, 17·5. $C_{13}H_{13}O_3N_3$ requires N, 17·3%).

α-*Benzoyl*-β-2-(6-*methoxynaphthyl*)-*ethylene*.—2-Methoxy-6-naphthaldehyde (2 g.) was treated with acetophenone (1 g.) and a solution of sodium (0·5 g.) in methanol (50 c.c.); on standing, a yellow precipitate separated. This was collected, washed with methanol and water, and dried. It crystallised from methanol in glistening pale yellow plates (2 g.), m. p. 144—145° (Found : C, 83·3; H, 5·6. $C_{20}H_{16}O_2$ requires C, 83·3; H, 5·6%).

α-*Anisoyl*-β-2-(6-*methoxynaphthyl*)-*ethylene*.—The reaction was carried out as above, using 2-methoxy-6-naphthaldehyde (2·0 g.) and *p*-methoxyacetophenone (1·6 g.). The solid was collected, washed, and dried. It crystallised from ethyl acetate in yellow needles (1·85 g., 60%), m. p. 166—167° (Found : C, 79·3; H, 6·2. $C_{12}H_{18}O_3$ requires C, 79·2; H, 5·7%).

p-*Methoxyphenyl* β-2-(6-*Methoxynaphthyl*)-*ethyl Ketone* (V).—The latter chalkone (1·73 g.) was hydrogenated in ethyl acetate (20 c.c.) in the presence of Adams' platinic oxide catalyst (0·25 g.) at room temperature and 1½ atm. When the necessary amount of hydrogen had been absorbed the liquid was filtered and ethyl acetate removed by evaporation from the colourless solution. The residue crystallised from methanol in colourless leaflets (1·6 g.), m. p. 104—105° (Found : C, 78·5; H, 6·75. $C_{21}H_{20}O_3$ requires C, 78·7; M, 6·4%).

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## 20. *Equilibria in Ternary Systems containing Oxalates.*

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Data are given for a number of isotherms in the systems : (1) oxalic acid–sodium oxalate–water at 0°, 25°, 60°, and 80°; (2) oxalic acid–sulphuric acid–water at 25° and 60°; (3) sodium sulphate–sodium oxalate–water at 25° and 60°. The results obtained at 25° agree in the main with those already published, but in some cases they are more complete.

In system (1) the hydrated double salt $H_2C_2O_4.Na_2C_2O_4.2H_2O$, which was known to exist at 25°, has been found to exist throughout the temperature range 0—80°. In system (2) the dehydration of hydrated oxalic acid by sulphuric acid is again a feature of the 60° isotherm.

The data include some additional determinations in the binary systems oxalic acid–water and sodium oxalate–water.

*System Oxalic Acid–Sodium Oxalate–Water*.—Data at 25° have been reported by Foote and Andrew (*Amer. Chem. J.*, 1905, **34**, 153, 165). The interesting feature of the system is the formation of the hydrated double

salt $H_2C_2O_4.Na_2C_2O_4.2H_2O$. Our work at 25° is in fair agreement with that already reported, and the additional isotherms at 0°, 60°, and 80° also show that the same compound is stable at these temperatures. The region of unsaturated solutions shows a considerable expansion as the temperature is raised from 0° to 80°; this is due to the rapid increase in the solubility of hydrated oxalic acid with rising temperature. It should be noted that the amount of sodium oxalate dissolved at 80° is insufficient to dehydrate the oxalic acid.

*System Oxalic Acid–Sulphuric Acid–Water.*—The main characteristic of this system is that we have two liquid components at the temperatures under investigation. Since oxalic acid is normally hydrated, the isotherm must contain at least two solubility curves, one starting from the solubility of hydrated oxalic acid in water and the other from the solubility of anhydrous oxalic acid in sulphuric acid. This system was studied at 25° by Elöd and Acker (*Z. anorg. Chem.*, 1928, **176**, 305), who gave data for the hydrate curve extending to the point of dehydration in a solution containing approximately 59% of sulphuric acid and 8% of oxalic acid. Our work at 25° agrees with their results and supplements it by data for the anhydrous oxalic acid curve over a large part of its course. Our isotherm at 60° is similar in character to that at 25° and shows that the dehydration of hydrated oxalic acid occurs at a lower concentration of sulphuric acid (45%). The solubility of anhydrous oxalic acid in sulphuric acid was not determined at 25° or 60° and no new solid phase has been observed.

*System Sodium Sulphate–Sodium Oxalate–Water.*—The published information on this system consists of the compositions of invariant solutions in equilibrium with sodium oxalate and sodium sulphate at 25° (Elöd and Acker, *loc. cit.*) and at 15° and 50° (Colani, *Bull. Soc. chim.*, 1916, **19**, 405). At 15° and 25° the sodium sulphate is hydrated (10 $H_2O$) and at 50° it is anhydrous. The system is characterised by the low solubility of sodium oxalate in a solution saturated with sodium sulphate. This was found to be true at 60° as well as at the lower temperatures. No intermolecular compounds or other complications were noted.

## Experimental.

The solubility mixtures were prepared from B.D.H. reagents of A.R. quality. In most cases it was possible to dissolve all the solids by a preliminary heating to a temperature above that of the required isotherm. This assisted the formation of the correct solid phase and helped to avoid inclusions of another solid within the newly formed crystals. Each mixture was put in a glass bottle fitted with a glass stirrer; the bottle and contents were then clamped in a bath of water and the temperature controlled within ±0·02° of that required. At 0° a stirred mixture of ice and water was used for the bath.

After stirring had proceeded long enough for the attainment of equilibrium (usually overnight), the solid was allowed to settle, and samples of the clear solution and moist solid were then withdrawn and analysed by means of methods selected from the following: (*a*) Total acidity by titration with N-sodium hydroxide solution (free from sodium carbonate) with phenolphthalein as indicator. (*b*) Oxalate by titration with 0·1N-potassium permanganate solution in the presence of sulphuric acid. (*c*) Sulphate gravimetrically as barium salt in the presence of hydrochloric acid. (*d*) Sodium by conversion into sulphate by sulphuric acid, and ignition to expel excess of acid. The methods used in each system are indicated at the foot of the tables: where the common ion was determined, the concentration of one component was obtained by difference.

The identity of each solid phase was determined graphically by the method of residues. Some of the tie lines are a little wide of the point representing possible solid phases, and these deviations may be emphasised by small analytical errors where one component has been determined by difference. As far as can be seen they have no special significance. In a few cases the identification of the solid phase was made by microscopic examination and these are indicated in the tables.

*System* $H_2C_2O_4$–$Na_2C_2O_4$–$H_2O$.

| Solid phase.* | $d^{t}_{15°}$. | Solution, g. per 100 g. | | Moist solid, g. per 100 g. | | Solid phase. | $d^{t}_{15°}$. | Solution, g. per 100 g. | | Moist solid, g. per 100 g. | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $H_2C_2O_4$. | $Na_2C_2O_4$. | $H_2C_2O_4$. | $Na_2C_2O_4$. | | | $H_2C_2O_4$. | $Na_2C_2O_4$. | $H_2C_2O_4$. | $Na_2C_2O_4$. |
| | Temperature = 0°. | | | | | | Temperature = 25°. | | | | |
| H | 1·013 | 3·4 | — | — | — | H | 1·043 | 10·2 | — | — | — |
| H + DS | 1·012 | 3·5 | 0·3 | 40·3 | 3·7 | H + DS | 1·046 | 10·3 | 1·0 | 34·7 | 3·10 |
| DS | 1·015 | 3·3 | 0·3 | 21·0 | 29·5 | H + DS | 1·049 | 10·3 | 1·0 | 27·9 | 25·3 |
| DS | — | 0·3 | 0·8 | 16·4 | 24·7 | DS | 1·044 | 8·8 | 0·9 | 24·0 | 31·3 |
| DS | 1·007 | 0·2 | 1·3 | 17·3 | 25·9 | DS | 1·027 | 5·3 | 1·0 | 21·7 | 30·7 |
| DS + N† | — | 0·1 | 2·9 | — | — | DS | 1·022 | 4·3 | 1·1 | 21·3 | 30·1 |
| | | 0·1 | 2·8 | | | DS + N | 1·025 | 0·4 | 3·7 | 2·7 | 31·8 |
| N † | — | — | 2·71 | — | — | N | 1·023 | — | 3·6 | — | — |
| | Temperature = 80°. | | | | | | Temperature = 60°. | | | | |
| H | — | 47·4 | — | — | — | H | 1·129 | 31·6 | — | — | — |
| H | — | 48·1 | 3·7 | 61·4 | 2·2 | H | 1·138 | 31·5 | 1·7 | 51·3 | 1·4 |
| H | — | 47·4 | 1·3 | 60·9 | 0·5 | H | 1·148 | 31·8 | 2·8 | 53·7 | 2·2 |
| H + DS | — | 48·2 | 4·9 | 56·7 | 9·1 | H + DS | 1·151 | 31·6 | 3·3 | 51·4 | 8·7 |
| DS | — | 47·3 | 4·5 | 41·2 | 29·3 | DS | 1·144 | 30·7 | 3·1 | 33·2 | 33·0 |
| DS | — | 37·5 | 5·2 | 36·3 | 32·0 | DS | 1·091 | 19·3 | 3·0 | 28·0 | 32·1 |
| DS | — | 29·6 | 5·2 | 32·7 | 29·4 | DS | 1·044 | 9·4 | 3·5 | 25·1 | 33·9 |
| DS | — | 22·2 | 5·4 | 29·4 | 30·1 | DS + N | 1·034 | 1·7 | 5·8 | 17·0 | 40·9 |
| DS | — | 10·0 | 5·4 | 25·0 | 34·2 | N | 1·028 | 1·1 | 5·3 | 0·5 | 54·9 |
| DS + N | — | 3·3 | 7·8 | 8·9 | 45·2 | N | 1·020 | — | 4·6 | — | — |
| N | — | 2·4 | 6·9 | 0·9 | 70·9 | | | | | | |
| N | — | 0·9 | 5·9 | 0·4 | 63·8 | | | | | | |
| N | — | — | 5·3 | — | — | | | | | | |

Analytical methods (*a*) and (*b*) were used.

* H = $H_2C_2O_4.2H_2O$; DS = $H_2C_2O_4.Na_2C_2O_4.2H_2O$; N = $Na_2C_2O_4$.

† Solid phases identified by the microscope.

*System* $H_2C_2O_4$–$H_2SO_4$–$H_2O$.

| Solid phase.* | $d_{15°}^{25°}$. | Solution, g. per 100 g. | | Moist solid, g. per 100 g. | | Solid phase. | $d_{15°}^{60°}$. | Solution, g. per 100 g. | | Moist solid, g. per 100 g. | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $H_2C_2O_4$. | $H_2SO_4$. | $H_2C_2O_4$. | $H_2SO_4$. | | | $H_2C_2O_4$. | $H_2SO_4$. | $H_2C_2O_4$. | $H_2SO_4$. |
| | Temperature = 25°. | | | | | | Temperature = 60°. | | | | |
| H | 1·043 | 10·2 | — | — | — | H | 1·129 | 31·6 | — | — | — |
| H | 1·078 | 6·6 | 9·6 | 54·4 | 2·2 | H | 1·150 | 25·2 | 7·2 | 57·4 | 1·8 |
| H | 1·119 | 4·7 | 15·4 | 54·8 | 3·6 | H | — | 20·2 | 14·2 | 53·4 | 4·4 |
| H | 1·165 | 3·6 | 21·5 | 47·6 | 7·1 | H | — | 16·6 | 20·2 | 52·9 | 6·4 |
| H | 1·174 | 2·9 | 29·5 | 49·8 | 8·7 | H | 1·294 | 12·3 | 33·2 | 50·3 | 11·2 |
| H | 1·272 | 2·3 | 38·6 | 41·6 | 16·5 | H | 1·334 | 12·1 | 38·5 | 51·1 | 13·1 |
| H | — | 2·6 | 47·1 | 24·2 | 32·0 | H | 1·387 | 13·1 | 43·5 | 50·4 | 14·9 |
| H | 1·469 | 4·6 | 55·1 | 25·2 | 37·9 | H | — | 15·1 | 44·9 | 51·2 | 15·2 |
| H + A | 1·516 | 7·8 | 59·6 | 48·3 | 31·9 | H + A | — | 20·5 | 44·6 | 64·6 | 12·6 |
| A | 1·600 | 5·2 | 67·4 | 39·9 | 42·0 | A | 1·469 | 19·4 | 46·4 | 69·9 | 16·9 |
| A | 1·662 | 4·0 | 74·4 | 34·9 | 50·4 | A | 1·493 | 16·5 | 50·5 | 63·4 | 21·7 |
| A | 1·771 | 4·1 | 85·9 | 39·9 | 53·6 | A | 1·514 | 13·9 | 55·6 | 65·7 | 21·6 |
| A | 1·788 | 4·6 | 89·9 | 32·7 | 63·5 | A | 1·583 | 9·5 | 65·0 | 61·1 | 27·6 |
| A | — | 4·6 | 91·6 | 32·8 | 64·2 | A | 1·610 | 8·6 | 67·7 | 57·6 | 31·5 |
| | | | | | | A | 1·673 | 7·2 | 79·6 | 59·4 | 34·8 |
| | | | | | | A | — | 8·3 | 84·0 | 34·5 | 59·9 |
| | | | | | | A | — | 7·6 | 71·2 | — | — |
| | | | | | | A | 1·704 | 8·7 | 86·5 | 51·9 | 45·4 |

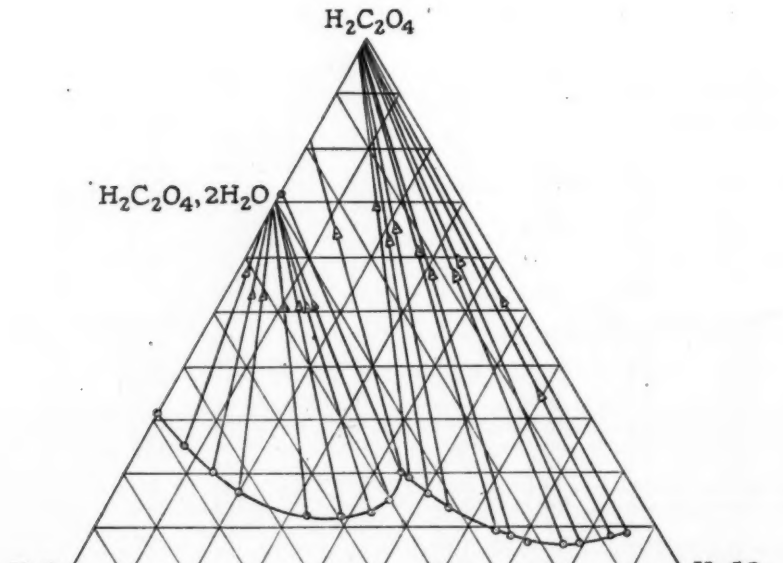
Analytical methods (*a*) and (*b*) were used.
* H = $H_2C_2O_4,2H_2O$; A = $H_2C_2O_4$.

*System* $Na_2SO_4$–$Na_2C_2O_4$–$H_2O$.

| Solid phase. | $d_{15°}^{25°}$. | Solution, g. per 100 g. | | Moist solid, g. per 100 g. | | Solid phase. | $d_{15°}^{60°}$. | Solution, g. per 100 g. | | Moist solid, g. per 100 g. | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $Na_2SO_4$. | $Na_2C_2O_4$. | $Na_2SO_4$. | $Na_2C_2O_4$. | | | $Na_2SO_4$. | $Na_2C_2O_4$. | $Na_2SO_4$. | $Na_2C_2O_4$. |
| | Temperature = 25°. | | | | | | Temperature = 60°. | | | | |
| S10 | 1·196 | 22·0 | — | — | — | S | — | 31·2 * | — | — | — |
| S10 + S | 1·200 | 22·0 | 0·5 | 33·0 | 4·9 | S + N | 1·289 | 30·7 | 0·3 | 57·7 | 30·0 |
| S | 1·182 | 19·7 | 0·5 | 10·9 | 46·5 | N | 1·269 | 28·6 | 0·4 | 9·0 | 62·6 |
| S | 1·155 | 14·7 | 0·8 | 7·5 | 54·6 | N | 1·177 | 20·2 | 0·7 | 6·4 | 70·0 |
| S | 1·060 | 5·9 | 1·7 | 2·7 | 55·8 | N | 1·088 | 10·1 | 1·7 | 3·5 | 66·8 |
| S | 1·023 | — | 3·6 | — | — | N | 1·020 | — | 4·6 | — | |

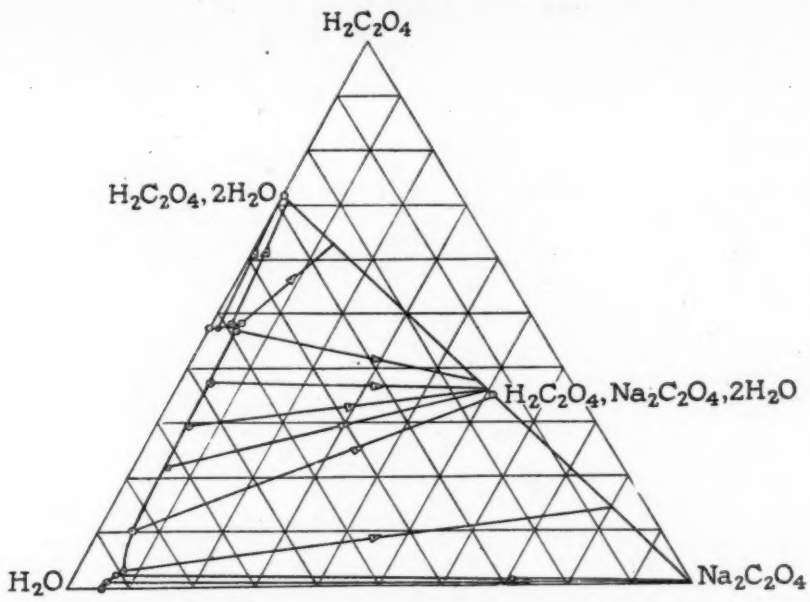
Analytical methods (*b*), (*c*), and (*d*) were used.
* S10 = $Na_2SO_4,10H_2O$; S = $Na_2SO_4$; N = $Na_2C_2O_4$.
† Seidell, "Solubilities of Inorganic and Metal Organic Salts," 1940, vol. 1, p. 1301.

FIG. 1.




The experimental results, expressed as g. per 100 g., are given in the tables, and representative triangular diagrams in Figs. 1 and 2.

FIG. 2.




The solution densities in the tables are approximate values only, determined in most cases by weighing the solution delivered at equilibrium temperature by a pipette which had been standardised with water at 15°.

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## 21. p-*Aminobenzenesulphonamide Derivatives of Pyrimidine as Antibacterial Agents.*

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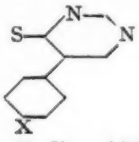
A number of sulphanilamides derived from aminopyrimidines have been prepared and investigated. Those from 2-amino-4 : 6-dialkoxypyrimidines showed unusual pharmacodynamic properties in that they were retained in the blood stream of experimental animals for an exceptional period of time. Exchange of one alkoxy group for another has been observed in the 2-amino-4 : 6-dialkoxypyrimidine series.

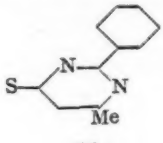
FOLLOWING the observation by Ewins, Phillips, and Newberry (B.P. 516,288) that the introduction of an α-pyridyl residue into the sulphonamide group of sulphanilamide led to an enhancement of antibacterial activity, many analogous preparations have been made with other heterocyclic systems. For a review of the literature up to 1940 see Northey, *Chem. Rev.*, 1940, **27**, 85.

In general, an effect similar to that observed in the case of sulphapyridine has been found with other analogous compounds containing heterocyclic rings particularly when the sulphonamido group was in the α-position to the tertiary nitrogen atom of the heterocyclic nucleus. The enhanced *in vivo* activity can be attributed to two factors, (*a*) an increase in the intrinsic antibacterial action of the drug as measured by increased *in vitro* activity and (*b*) an improvement in pharmacological properties resulting in the attainment of a higher concentration of the drug in the blood or tissues of the infected host. The incidence of these two factors is particularly marked in the case of the sulphanilamides derived from 2-aminopyrimidine (see, for example, Schmidt, Hughes, Badger, and Schmidt, *J. Pharmacol.*, 1944, **81**, 17; Schmidt, Sealer, and Hughes, *ibid.*, p. 43). Compounds of this type were first described by Roblin, Williams, Winnek, and English (*J. Amer. Chem. Soc.*, 1940, **62**, 2002) who prepared them by interaction of *p*-nitrobenzenesulphonyl chloride and aminopyrimidines followed by reduction of the nitro group. A different route, involving reaction of a *p*-substituted benzenesulphonylguanidine with a β-diketone or β-ketocarboxylic ester, has also been described by Rose and Swain (*J.*, 1945, 689) and others. A very considerable number of sulphanilamidopyrimidines are described in the literature and, although antibacterial activity is not recorded in every instance, it is possible to generalise to a limited extent on the relation between chemical structure and biological effect. 2-*p*-Aminobenzenesulphonamidopyrimidine (" sulphadiazine ") exhibits a high degree of antibacterial activity *in vitro* and persistence in the blood stream of experimental animals. The introduction of a methyl group into position 4- of the pyrimidine nucleus (" sulphamerazine ") is said to produce an even more persistent drug. Two methyl groups in positions 4- and 6- (IV : " sulphamezathine ") reduce intrinsic antibacterial activity somewhat,

but a marked increase in water solubility minimises the incidence of renal blockage during clearance from the animal body. Further chemical variations of the parent compound have been described (see for example, Caldwell, Kornfeld, and Donnell, *J. Amer. Chem. Soc.*, 1941, **63**, 2188; Sprague, Kissinger, and Lincoln, *ibid.*, 1941, **63**, 3028; G. de Sütö-Nagy and Johnson, *ibid.*, 1941, **63**, 3234; Joiner and Spoerri, *ibid.*, 1941, **63**, 1929; Roblin, Winnek, and English, *ibid.*, 1942, **64**, 567; Anderson, Faith, Marson, Winnek, and Roblin, *ibid.*, 1942, **64**, 2902; Backer and Grevenstuck, *Rec. trav. chim.*, 1942, **61**, 291), but no compound having improved properties appears to have been obtained. Nevertheless, we have continued during the past few years investigations of this type of sulphanilamide, and now record the chemical work with brief description of biological activity. Only sulphonamides derived from 2-amino- and 4-amino-pyrimidines have been examined and the emphasis has been on compounds which would exhibit favourable pharmacological properties. It appeared that the 4-*p*-aminobenzenesulphonamidopyrimidines were deficient in this respect (Roblin, Winnek, and English, *loc. cit.*), but it was considered that the introduction of substituents such as phenyl into the pyrimidine nucleus might overcome the defect. Suitably substituted aminopyrimidines have been described by Davies and Piggot (*J.*, 1945, 347) and Davies, Johnson, and Piggott (*ibid.*, p. 352), and the compounds (I) have been prepared by reaction with *p*-nitrobenzenesulphonyl chloride followed by reduction of the nitro group.



(X = H, Cl, and MeO).
(I.)



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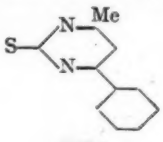

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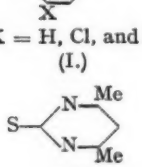

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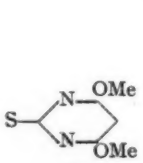

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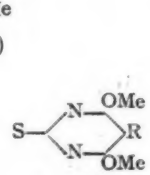

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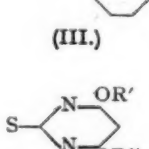
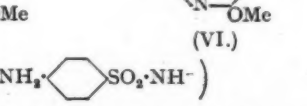


(VII.)



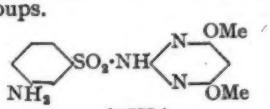
The related compound (II) and the 2-sulphanilamido derivative (III) were prepared in a similar manner. These compounds have been examined by Dr. A. R. Martin for *in vitro* and *in vivo* activity against the hæmolytic streptococcus. Only (I, X = H) was more effective than sulphanilamide and this substance was also more persistent in the blood stream of mice than the latter drug. It is, however, only sparingly soluble in water (3·5 mg./100 c.c. at 37°).

In view of the interest, already mentioned, in 2-sulphanilamido-4 : 6-dimethylpyrimidine (IV), an analogous preparation (V) was made in which the methyl groups were replaced by methoxyl. Related compounds containing one methoxyl group substituted into the pyrimidine nucleus have been described by Roblin, Winnek, and English (*loc. cit.*) but do not appear to have been of special interest. Compound (V), however, exhibited a higher degree of persistence in the blood stream of mice than any other sulphanilamide drug examined in these laboratories. It was also more active *in vitro* against experimental streptococcal infections. This substance was also unusual in that its acetyl derivative, although devoid of *in vitro* activity, was almost as effective *in vivo* as the free amine. This was shown to be due to a rapid de-acetylation in the animal body. These results will be published in detail elsewhere. The parent 2-amino-4 : 6-dimethoxypyrimidine was described by Fisher and Johnson (*J. Amer. Chem. Soc.*, 1932, **54**, 727); it was made by heating 4 : 6-dichloro-2-aminopyrimidine and sodium methoxide under pressure at 160—170°. It has now been shown that this reaction, which proceeds by stepwise replacement of the chlorine atoms, can be effected at atmospheric pressure. The first chlorine atom was rapidly replaced by methoxyl by heating in excess of methanol or more slowly by stirring the reactants together at room temperature. Addition of xylene to the reaction mixture and removal of the excess alcohol by distillation, finally refluxing for some hours, gave a 77·5% yield of the dimethoxy derivative. The aminopyrimidine was converted into the sulphanilamide by allowing it to react with 4-nitro- or 4-acetamido-benzenesulphonyl chloride and reducing or hydrolysing the resulting product; the second method gave the better yield.

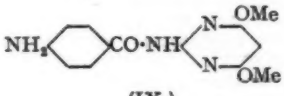
The high antibacterial activity of (V) led us to prepare other dialkoxy compounds of the same type. Thus methyl and ethyl were introduced into the 5-position of the pyrimidine nucleus (VI : R = Me or Et). As in the case of type (IV) (Rose and Swain, *loc. cit.*) such substitution led to a marked reduction in solubility in water. Compound (VI, R = Et) was sparingly soluble, and so were its sodium salt and hydrochloride. The parent aminopyrimidines were made in a manner analogous to that used for (V) by condensing the appropriately substituted ethyl malonate with guanidine, converting the product into the dichloro compound by means of phosphoryl chloride and into the final substance by the action of sodium methoxide in boiling xylene. Higher homologues of (V) (VII, R′ = R″ = Et, $Pr^{\alpha}$, $Pr^{\beta}$, $Bu^{\alpha}$, $-C_2H_4\cdot O\cdot Et$) were prepared similarly through the corresponding *p*-nitrobenzenesulphonamides, followed by reduction of the nitro group. Where R′ = R″ = $Bu^{\alpha}$ or $-C_2H_4\cdot O\cdot Et$ the final products were most conveniently isolated as the sodium salts. Compounds of type (VII, R′ = R″) were also prepared as follows: 4-chloro-2-amino-6-methoxypyrimidine was treated with

the higher sodium alkoxides by heating in excess of the corresponding alcohol or in xylene. In all cases examined (ethoxide, propoxide, butoxide), the dialkoxypyrimidines isolated from the reaction mixtures were mainly the symmetrical 4 : 6-diethoxy, dipropoxy and dibutoxy derivatives, respectively. It was apparent, therefore, that replacement of the methoxy group by the higher alkoxy groups had occurred, analogous to the ester interchange reaction in the carboxylic acid series. This phenomenon emphasised the essentially acid character of the hydroxyl groups substituted in the 4- and 6-positions of pyrimidine. Further experiments showed that the converse replacement of higher by lower alkoxy groups was possible, since 4-chloro-2-amino-6-ethoxypyrimidine gave considerable amounts of the dimethoxy derivative when treated with sodium methoxide in excess methanol. This suggested that the final reaction products constituted an equilibrium mixture the nature of which depended on which alcohol or alkoxide was present in excess; in accordance with this it was subsequently found that reaction of 4-chloro-2-amino-6-methoxypyrimidine with rather less than a molar quantity of sodium ethoxide in the absence of excess ethanol, gave substantial yields of the required asymmetric 2-amino-4-methoxy-6-ethoxypyrimidine. This compound was converted to its sulphanilamide derivative through condensation with *p*-acetamidobenzenesulphonyl chloride.

Biological examination of compounds (VI) and (VII) has shown them to be less effective than (V) against infections in mice, although all retain a high degree of persistence in the blood of the experimental animal, but at a lower average level than that given by (V). The reason for the unique pharmacological properties of this type of substance is now being investigated. It was thought, however, that some preliminary insight into the phenomenon might be gained by examination of compounds such as (VIII) and (IX), which would indicate how far the persistence effect was due to the 2-amido-4 : 6-dimethoxypyrimidine moiety or to the sulphanilamide structure as a whole. These compounds were made by condensation of the aminopyrimidine with *m*-nitrobenzenesulphonyl chloride and *m*-nitrobenzoyl chloride, respectively, and reduction of the nitro groups.



(VIII.)



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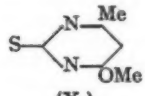
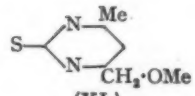


(X.)



(XI.)

Only (VIII) behaved similarly to (V) indicating that the sulphonamide group may be essential but that the primary amino group need not be in the *para* position. In this connection it should be noted that *p*-aminobenzoic acid is very rapidly removed from the blood stream of mice (Martin and Rose, *Biochem. J.*, 1945, **39**, 91). Two further compounds (X) and (XI) bearing some relation to (V), in that both carry methoxy substituents, were made.

Compound (X) was prepared by the method used for the preparation of (VIII), and (XI) was made by condensation of *p*-aminobenzenesulphonylguanidine (" sulphaguanidine ") with 1-methoxypentane-2 : 4-dione in the manner described by Rose and Swain (*loc. cit.*). The same compound prepared by the sulphonyl chloride route has been described by Backer and Grevenstuck (*loc. cit.*). Neither (X) nor (XI) was superior to sulphanilamide in antibacterial activity.

## Experimental.

*2-Aminopyrimidine Intermediates.*—*2-Amino-4 : 6-dimethoxypyrimidine.* Sodium (9·6 g.) was dissolved in methanol (160 c.c.), dry xylene (160 c.c.) added followed by 4 : 6-dichloro-2-aminopyrimidine (32·8 g., Büttner, *Ber.*, 1903, **36**, 2228). After the initial vigorous reaction, the mixture was heated in an oil-bath at 140—150° for 3 hours, allowing the methanol to distil away, benzene (100 c.c.) and water (200 c.c.) added and, after filtration, the benzene layer was distilled away. 2-Amino-4 : 6-dimethoxypyrimidine distilled at 252°/760 mm. (24 g., m. p. 92—93°). The *picrate*, prepared in methanol, crystallised from methanol–β-ethoxyethanol in yellow needles, m. p. 208° (Found : N, 21·9. $C_6H_9O_2N_3.C_6H_3O_7N_3$ requires N, 21·8%). According to Fisher and Johnson (*loc. cit.*) the base has m. p. 95°.

*2-Amino-4 : 6-diethoxypyrimidine* was prepared similarly from sodium (7·2 g.), ethanol (75 c.c.), xylene (50 c.c.) and 4 : 6-dichloro-2-aminopyrimidine (24·6 g.); it distilled at 265—266°/760 mm. (21·2 g., colourless crystals, m. p. 101°, from benzene) (Found : C, 51·85; H, 7·1; N, 22·5. $C_8H_{13}O_2N_3$ requires C, 52·4; H, 7·1; N, 22·9%). The *picrate*, prepared in methanol, crystallised from ethanol in yellow needles, m. p. 162° (Found : N, 20·15. $C_8H_{13}O_2N_3.C_6H_3O_7N_3$ requires N, 20·3%).

*2-Amino-4 : 6-di-n-propoxypyrimidine* was prepared from sodium (4·6 g.), *n*-propanol (100 c.c.), xylene (50 c.c.), and 4 : 6-dichloro-2-aminopyrimidine (16·5 g.); it distilled at 184°/42 mm. (16 g., colourless crystals, m. p. 72°, from ligroin) (Found : C, 57·05, H, 7·8; N, 19·45. $C_{10}H_{17}O_2N_3$ requires C, 56·9; H, 8·1; N, 19·9%). The *picrate*, prepared in methanol, crystallised from β-ethoxyethanol in yellow needles, m. p. 188° (Found : N, 19·15. $C_{10}H_{17}O_2N_3.C_6H_3O_7N_3$ requires N, 19·1%).

*2-Amino-4 : 6-di-isopropoxypyrimidine* was prepared using quantities as for *n*-propoxy derivative; it distilled at 160°/30 mm. (13·8 g., colourless crystals, m. p. 90°, from ligroin) (Found : C, 56·55; H, 7·55; N, 19·35. $C_{10}H_{17}O_2N_3$ requires C, 56·9; H, 8·1; N, 19·9%). The *picrate*, prepared in and recrystallised from methanol, formed yellow needles, m. p. 108° (Found : N, 19·1. $C_{10}H_{17}O_2N_3.C_6H_3O_7N_3$ requires N, 19·1%).

*2-Amino-4 : 6-di-n-butoxypyrimidine*, prepared from sodium (7·2 g.), *n*-butanol (150 c.c.), xylene (50 c.c.), and 4 : 6-dichloro-2-aminopyrimidine (24·6 g.), distilled at 192°/17 mm. (27·9 g., colourless needles, m. p. 58°, from ligroin) (Found : C, 60·3; H, 8·45; N, 17·35. $C_{12}H_{21}O_2N_3$ requires C, 60·2; H, 8·8; N, 17·6%). The *picrate*, prepared in and recrystallised from methanol, formed yellow needles, m. p. 182—183° (Found : N, 17·75. $C_{12}H_{21}O_2N_3.C_6H_3O_7N_3$ requires N, 17·9%).

*2-Amino-4 : 6-di-(β-ethoxyethoxy)-pyrimidine.* Sodium (4·6 g.) was dissolved in β-ethoxyethanol (70 c.c.) and 4 : 6-dichloro-2-aminopyrimidine (16·5 g.) added. After the initial vigorous reaction the mixture was heated for 4 hours in an oil-bath 160—180°. Excess β-ethoxyethanol was removed under reduced pressure, the residue treated with water, extracted twice with ether, and the ether layer distilled. The aminopyrimidine boiled at 228—230°/12 mm. (24 g.

colourless viscous liquid). The *picrate*, prepared in methanol, crystallised from aqueous methanol in yellow needles, m. p. 121° (Found : C, 42·9; H, 4·55; N, 16·45. $C_{12}H_{21}O_4N_3,C_6H_3O_7N_3$ requires C, 43·2; H, 4·8; N, 16·8%).

4-*Chloro*-2-*amino*-6-*methoxypyrimidine*. Sodium (23 g.) was dissolved in methanol (300 c.c.), 4 : 6-dichloro-2-aminopyrimidine (82 g. finely powdered) added, the suspension was stirred at laboratory temperature for 24 hours and filtered. The solid was washed with methanol, then with water to remove sodium chloride and dried at 60° (63 g., m. p. 159—162°). It crystallised from toluene (500 c.c.) in colourless needles (47 g., m. p. 164—166°) (Found : Cl, 22·7. Calc. for $C_5H_6ON_3Cl$:Cl, 22·3%). Gabriel and Colman (*Ber.*, 1903, **36**, 3381) give m. p. 168—169°.

4-*Chloro*-2-*amino*-6-*ethoxypyrimidine*, prepared similarly from sodium (3·5 g.), ethanol (100 c.c.), and 4 : 6-dichloro-2-aminopyrimidine (16·4 g.), was isolated from the alcoholic filtrate by adding water (500 c.c.) and crystallised twice from ligroin (6 g., colourless prisms, m. p. 87°) (Found : Cl, 21·0; N, 23·85. $C_6H_8ON_3Cl$ requires Cl, 20·95; N, 24·1%).

2-*Amino*-4-*methoxy*-6-*ethoxypyrimidine*. (i) A mixture of sodium (4·4 g.) in ethanol (60 c.c.) and xylene (50 c.c.) with 4-chloro-2-amino-6-methoxypyrimidine (15 g.) was heated in an oil-bath at 170° for 8 hours, the alcohol being allowed to distil away. The only isolated product, obtained as above, was 2-amino-4 : 6-diethoxypyrimidine (7·7 g., m. p. 101—102°, undepressed in admixture with authentic sample). A similar experiment in which methanol replaced ethanol and 4-chloro-2-amino-6-ethoxypyrimidine the corresponding methoxy derivative gave, likewise, 2-amino-4 : 6-dimethoxypyrimidine (3·3 g., m. p. 91°; undepressed in admixture with authentic sample). It was probable that in both cases the required methoxyethoxy pyrimidine was formed to some extent during the reactions but was not isolated. (ii) Sodium (2·5 g.) was dissolved in a mixture of ethanol (17 c.c.) and xylene (50 c.c.) and the excess alcohol distilled away. 4-Chloro-2-amino-6-methoxypyrimidine (17·5 g.) was added, the mixture was refluxed for 2 hours and, after diluting with benzene, was extracted with hydrochloric acid (200 c.c., 5N). The aqueous layer was made alkaline with sodium hydroxide, the precipitated oil taken into ether, dried over potassium hydroxide and distilled. The fraction boiling at 226—228°/736 mm. was collected (9·7 g.), crystallised from ligroin and twice from water. 2-*Amino*-4-*methoxy*-6-*ethoxypyrimidine* formed colourless needles, m. p. 98° (Found : N, 24·4. $C_7H_{11}O_2N_3$ requires N, 24·8%). The *picrate*, prepared in ethanol, crystallised from water in yellow plates, m. p. 185—186° (Found : C, 39·05; H, 3·95; N, 21·4. $C_7H_{11}O_2N_3,C_6H_3O_7N_3$ requires C, 39·2; H, 3·6; N, 21·1%).

2-*Amino*-4 : 6-*dimethoxy*-5-*methylpyrimidine*. 4 : 6-Dichloro-2-amino-5-methylpyrimidine (10·9 g., prepared by the method of Gabriel and Colman starting with diethyl α-methylmalonate in place of diethyl malonate), sodium (4·3 g.) in methanol (45 c.c.) and xylene (50 c.c.) were heated together for 4 hours in an oil-bath at 160—170°. The reaction mixture, worked up as above, gave 2-*amino*-4 : 6-*dimethoxy*-5-*methylpyrimidine* in colourless crystals (5 g., m. p. 112—114°) from ligroin (Found : N, 24·6. $C_7H_{11}O_2N_3$ requires N, 24·8%).

2-*Amino*-4 : 6-*dimethoxy*-5-*ethylpyrimidine*, prepared analogously, gave colourless crystals, m. p. 92—94°, from ligroin (Found : N, 22·55. $C_8H_{13}O_2N_3$ requires N, 22·95%).

*Sulphanilamide Derivatives*.—2-p-*Aminobenzenesulphonamido*-4 : 6-*dimethoxypyrimidine* (V). (i) 2-Amino-4 : 6-dimethoxypyrimidine (15·5 g.), *p*-acetamidobenzenesulphonyl chloride (23·4 g.), and pyridine (30 c.c.) were mixed and heated at 60—70° for 1 hour, then at 40° for 16 hours. The granular mass, obtained on adding water, was purified by boiling with a mixture of methanol (50 c.c.) and water (20 c.c.) and recrystallised from aqueous β-ethoxyethanol giving 2-p-*acetamidobenzenesulphonamido*-4 : 6-*dimethoxypyrimidine*, m. p. 235° (Found : N, 16·1. $C_{14}H_{16}O_5N_4S$ requires N, 15·9%). The acetyl group was removed by boiling with N-NaOH (200 c.c.) for 6 hours and treating the product with decolorising charcoal successively in alkaline and in hydrochloric acid solution, finally precipitating with ammonia. 2-p-*Aminobenzenesulphonamido*-4 : 6-*dimethoxypyrimidine* gave colourless crystals, m. p. 171·5°, from methanol (Found : C, 46·75; H, 4·9; N, 17·85; MeO, 19·7. $C_{12}H_{14}O_4N_4S$ requires C, 46·5; H, 4·5; N, 18·1; MeO, 20·0%). (ii) 2-Amino-4 : 6-dimethoxypyrimidine (3·1 g.), *p*-nitrobenzenesulphonyl chloride (4·5 g.) and pyridine (5 c.c.) were mixed, warmed to 60°, and then set aside at 20° for 48 hours. The resultant paste was washed with water by decantation, dissolved in cold dilute sodium hydroxide, decolorised with charcoal and neutralised with acetic acid. The precipitate was dried (3·9 g.). The crude nitro compound (6·8 g.) was reduced by refluxing for 6 hours with iron filings (6 g.) in β-ethoxyethanol (20 c.c.) and concentrated hydrochloric acid (0·5 c.c.). The reduction mixture was added to water (200 c.c.) containing 2N-sodium carbonate (25 c.c.) and filtered. The filtrate was neutralised with acetic acid. The precipitate (tar + crystals), formed on standing, was purified by solution successively in dilute hydrochloric acid and sodium hydroxide. The product was contaminated with coloured impurities and only after repeated crystallisation from methanol had m. p. 175·5°, undepressed in admixture with material made by method (i).

2-p-*Aminobenzenesulphonamido*-4 : 6-*diethoxypyrimidine* (VII, R′ = R″ = Et), prepared by method (ii), the intermediate nitro derivative (crystallised, m. p. 156°, from ethanol) being reduced in ethanol, gave colourless crystals, m. p. 140°, from aqueous β-ethoxyethanol (Found : N, 15·4; S, 8·85. $C_{14}H_{18}O_4N_4S,2H_2O$ requires N, 15·0; S, 8·55%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*di*-n-*propoxypyrimidine* (VII, R′ = R″ = $Pr^n$), prepared by method (ii) (effecting the reduction of the nitro compound in *n*-propanol in place of β-ethoxyethanol), gave colourless crystals, m. p. 128—129°, from methanol (Found : N, 15·25; S, 8·75. $C_{16}H_{22}O_4N_4S$ requires N, 15·3; S, 8·75%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*di*-iso*propoxypyrimidine* (VII, R′ = R″ = $Pr^\beta$), prepared similarly to *n*-propoxy derivative and crystallised from methanol, had m. p. 159—160° after drying under reduced pressure at 80° (Found : N, 15·25; S, 8·9. $C_{16}H_{22}O_4N_4S$ requires N, 15·3; S, 8·75%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*di*-n-*butoxypyrimidine* (VII, R′ = R″ = $Bu^n$) was prepared by method (ii). The intermediate nitro derivative was purified through its sparingly soluble *sodium salt*; yellow leaflets, m. p. 140°, from aqueous methanol (Found : C, 46·6; H, 5·6; S, 6·9; Na, 4·65. $C_{18}H_{22}O_4N_4SNa,H_2O$ requires C, 46·5; H, 5·4; S, 6·9; Na, 4·95%). The reduction of the nitro compound was carried out in butanol in place of β-ethoxyethanol; this allowed the sodium salt of the amine to crystallise from the hot alkaline filtrate; colourless crystals, m. p. 275° (after drying at 110°), from butanol (Found : C, 48·45; H, 5·95; N, 12·9; S, 7·3; Na, 5·4. $C_{18}H_{25}O_4N_4SNa,1\frac{1}{2}H_2O$ requires C, 48·7; H, 6·3; N, 12·65; S, 7·2; Na, 5·2%).

2-p-*Aminobenzenesulphonamido*-4-*methoxy*-6-*ethoxypyrimidine* (VII, R′ = Me, R″ = Et) was prepared by a modification of method (i). The intermediate acetamido derivative was not isolated but was hydrolysed directly by adding 12 equivalents of 5N-NaOH and distilling away the pyridine in steam during 20 minutes. The crude base was precipitated with acetic acid and purified by clarifying successively the solutions in dilute hydrochloric acid and dilute aqueous ammonia, finally crystallising from benzene; colourless prisms, m. p. 127—128° (Found : C, 48·5; H, 4·65; N, 17·1. $C_{13}H_{16}O_4N_4S$ requires C, 48·2; H, 4·9; N, 17·3%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*dimethoxy*-5-*methylpyrimidine* (VI, R = Me) was prepared similarly by the modification of method (i). The amine was isolated as its sodium salt on cooling after steam distillation of the pyridine; it was dissolved in hot water, converted into free sulphonamide with acetic acid, and recrystallised from aqueous dioxan; it had m. p. 227—228° (Found : S, 9·6. $C_{13}H_{16}O_4N_4S$ requires S, 9·85%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*dimethoxy*-5-*ethylpyrimidine* (VI, R = Et) was prepared and isolated analogously; it was crystallised from *o*-dichlorobenzene (or aqueous dioxan) and obtained in colourless plates, m. p. 234—236° (Found : S, 9·2. $C_{14}H_{18}O_4N_4S$ requires S, 9·45%); it was not readily soluble either in dilute acids or in alkalis.

4-p-*Aminobenzenesulphonamido*-5-*phenylpyrimidine* (I, X = H). *p*-Nitrobenzenesulphonyl chloride (4·5 g.) was

condensed with 4-amino-5-phenylpyrimidine (3·4 g., Davies *et al.*, *loc. cit.*) in pyridine (10 c.c.) on the water-bath for 2 hours. The crude nitro compound obtained on adding dilute hydrochloric acid was partly purified by extraction with dilute sodium hydroxide and reprecipitation with acid, and reduced by refluxing for 3·5 hours in water (50 c.c.), concentrated hydrochloric acid (2 c.c.) and iron filings (10 g.). The base was isolated by making alkaline with sodium hydroxide, filtering and neutralising the filtrate with acetic acid. It formed colourless plates from aqueous β-ethoxyethanol, m. p. 253—255° (Found: N, 17·2. $C_{16}H_{14}O_2N_4S$ requires N, 17·2%).

4-p-*Aminobenzenesulphonamido*-5-p-*anisylpyrimidine* (I, X = OMe), colourless needles from aqueous β-ethoxyethanol, m. p. 269° (Found: N, 16·25. $C_{17}H_{16}O_3N_4S$ requires N, 16·5%), and 4-p-*aminobenzenesulphonamido*-5-p-*chlorophenylpyrimidine* (I, X = Cl), colourless prisms from aqueous β-ethoxyethanol, m. p. 267° (Found: N, 15·05. $C_{16}H_{13}O_2N_4SCl$ requires N, 15·2%), were prepared analogously.

2-p-*Aminobenzenesulphonamido*-4-*phenyl*-6-*methylpyrimidine* (III), prepared by method (ii) from 2-amino-4-phenyl-6-methylpyrimidine (Evans, *J. pr. Chem.*, 1893, **48**, 513), formed colourless crystals from β-ethoxyethanol, m. p. 236° (Found: C, 60·2; H, 4·65; N, 16·3. $C_{17}H_{16}O_2N_4S$ requires C, 60·0; H, 4·7; N, 16·45%).

6-p-*Aminobenzenesulphonamido*-2-*phenyl*-4-*methylpyrimidine* (II), prepared by method (ii) from 6-amino-2-phenyl-4-methylpyrimidine (Pinner, *Ber.*, 1887, **20**, 2363), was recrystallised from ethanol. It had m. p. 210—211° (Found: N, 16·35. $C_{17}H_{16}O_2N_4S$ requires N, 16·45%).

2-p-*Aminobenzenesulphonamido*-4-*methoxy*-6-*methylpyrimidine* (X), prepared by method (ii) from 2-amino-4-methoxy-6-methylpyrimidine (m. p. 154—155°, from the chloro compound and sodium methoxide) and reducing the intermediate nitro derivative (m. p. 256°) with iron filings in β-ethoxyethanol, formed colourless crystals from methanol, m. p. 195° (Found: C, 48·95; H, 5·2; N, 18·4. $C_{12}H_{14}O_3N_4S$ requires C, 49·0; H, 4·5; N, 19·0%).

2-p-*Aminobenzenesulphonamido*-6-*methyl*-4-*methoxymethylpyrimidine* (XI). *p*-Aminobenzenesulphonylguanidine (4·3 g.), 1-methoxypentane-2 : 4-dione (3·4 g., prepared by a method analogous to that used by Sommelet (*Bull. Soc. chim.*, 1907, **4**, 382) for the ethoxy compound), amyl alcohol (6 c.c.), and acetic acid (2 c.c.) were heated together for 16 hours in an oil-bath at 150°. A dilute sodium hydroxide extract of the reaction mixture was clarified with decolorising charcoal and neutralised with dilute acid. The semi-solid precipitate crystallised when stirred with methanol and was recrystallised from the same solvent, giving 1·1 g., m. p. 167—170° (Found: C, 51·05; H, 5·75; N, 17·8; MeO, 10·1. $C_{13}H_{16}O_3N_4S$ requires C, 50·7; H, 5·2; N, 18·2; MeO, 9·75%).

*Miscellaneous Amides.*—2-m-*Aminobenzenesulphonamido*-4 : 6-*dimethoxypyrimidine* (VIII). *m*-Nitrobenzenesulphonyl chloride (11·1 g.), 2-amino-4 : 6-dimethoxypyrimidine (8·5 g.) and pyridine (50 c.c.) were kept at 90° for 1 hour. The reaction mixture was stirred with dilute hydrochloric acid and the dark gummy residue was dissolved in dilute sodium hydroxide, clarified with decolorising charcoal, and the precipitate with acetic acid collected and crystallised from aqueous β-ethoxyethanol (3·0 g., m. p. 149—151°). This was reduced in methanol solution with hydrogen at atmospheric temperature and pressure in the presence of nickel. The residue after filtration from catalyst and distillation of the solvent, crystallised in colourless needles from butanol (1·2 g., m. p. 134°) (Found: N, 17·75. $C_{12}H_{14}O_4N_4S$ requires N, 18·1%).

2-p-*Aminobenzamido*-4 : 6-*dimethoxypyrimidine* (IX). *p*-Nitrobenzoyl chloride (9·3 g.), 2-amino-4 : 6-dimethoxypyrimidine (7·8 g.) and pyridine (20 c.c.) were mixed at 50—60° and then kept at 40° for 16 hours. Water (100 c.c.) was added, the precipitate stirred in boiling ethanol (30 c.c.), and the suspension cooled and filtered. The crude nitro compound (11·8 g.) was reduced with iron filings (12 g.) by refluxing for 6 hours in ethanol (150 c.c., 95%) and concentrated hydrochloric acid (0·5 c.c.). Sodium carbonate was then added and the hot suspension filtered. The filtrate was evaporated to dryness, the residue digested in cold dilute sodium hydroxide, filtered and reprecipitated with acetic acid. The solid, crystallised from aqueous β-ethoxyethanol (charcoal), gave 4·4 g., m. p. 191° (Found: C, 57·45; H, 5·55; N, 19·8. $C_{13}H_{14}O_3N_4$ requires C, 57·0; H, 5·1; N, 20·4%).

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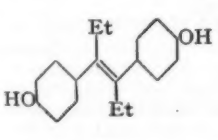
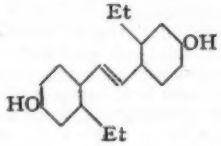
## 22. *New Synthetic Oestrogens. Part I. The Synthesis of* 4 : 4′-*Dihydroxy*-α : β : 2 : 2′-*tetramethylstilbene and* 4 : 4′-*Dihydroxy*-α : β : 2 : 2′-*tetramethyldibenzyl.*

By B. J. F. HUDSON and E. WALTON.

The synthesis of a new stilboestrol analogue, 4 : 4′-*dihydroxy*-α : β : 2 : 2′-*tetramethylstilbene* (III), and a new synthesis of the corresponding hexoestrol analogue, 4 : 4′-dihydroxy-α : β : 2 : 2′-tetramethyldibenzyl (Bretschneider, de Jonge-Bretschneider, and Ajtai, *Ber.*, 1941, **74**, 571), are described. Both these substances have oestrogenic activity.

THERE is evidence that the physiological properties of stilboestrol (I) and hexoestrol can be attributed, at least in part, to their close structural relationship to the natural oestrogens (Dodds, Golberg, Lawson, and Robinson, *Proc. Roy. Soc.*, B, 1939, **127**, 140). On these grounds one might reasonably expect oestrogenic activity to be shown by the appropriately substituted nuclear-alkyl (stilbene) analogues of stilboestrol (II—VI) :


(I.)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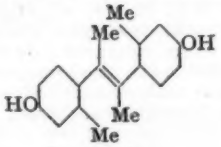
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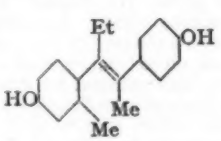
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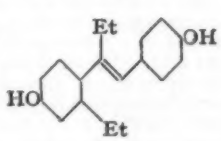
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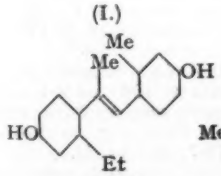
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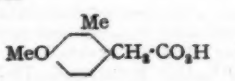
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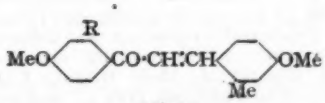
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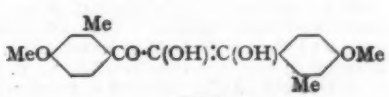
(IX.)

Of these compounds Linnell and Shaikmahamud (*Quart. J. Pharm.*, 1942, **15**, 384) have prepared (II) by the treatment of *o*-ethylthioanisaldehyde with copper-bronze, followed by demethylation, but their product had only one thousandth of the activity of stilboestrol. B. R. Baker (*J. Amer. Chem. Soc.*, 1943, **65**, 1572) prepared the reduced form of (II) (4 : 4′-dihydroxy-2 : 2′-diethyldibenzyl) by heating the dihydroaldazine of 4-methoxy-2-ethylbenzaldehyde, followed by demethylation. This substance was reported to be entirely inactive.

Compounds (III—VI) have not hitherto been described, but Bretschneider *et al.* (*Ber.*, 1941, **74**, 571) have prepared the reduced form of (III), a hexoestrol analogue (probably the *meso*-stereoisomer), by the dihydroazine synthesis, starting with 4-hydroxy-2-methylacetophenone. Their compound was believed to be accompanied by its *dl*-stereoisomer, though the latter was not isolated. It was found to be slightly less active than hexoestrol when the two substances were compared in the Allen and Doisy test.

We have now prepared (III) by a well-known series of reactions (alkylation, Grignard reaction, dehydration and demethylation) from 2 : 2′-*dimethyldeoxyanisoin*. This intermediate ketone was obtained by a Friedel–Crafts condensation of *m*-methylanisole with the acid chloride of *4-methoxy-2-methylphenylacetic acid* (VII), which was itself prepared from 4-methoxy-2-methylbenzaldehyde by the " azlactone " synthesis. By hydrogenation of the oily modification of the *dimethyl ether* of (III) a crystalline compound, apparently identical with the dimethyl ether prepared by Bretschneider *et al.* (*loc. cit.*), was obtained. It moreover afforded a diphenol, and the latter a diacetate, both agreeing in properties with the corresponding compounds described by these authors.

A more obvious approach to (III) would be through the product of a benzoin condensation using 4-methoxy-2-methylbenzaldehyde. Repeated attempts to obtain 2 : 2′-dimethyldeoxyanisoin by this method have, however, not yielded the expected product. Apart from unchanged aldehyde, only a very small quantity of a substance, possibly 2 : 2′-*dimethylanisil*, has been isolated. It would appear that Linnell and Shaikmahamud (*loc. cit.*) in their attempted preparation of 2 : 2′-diethylanisoin have encountered a similar difficulty.

In view of the length of the method finally adopted for 2 : 2′-dimethyldeoxyanisoin (see above), attempts were made to shorten the process by utilising the chalkone, *αγ-di-(4-methoxy-2-methylphenyl)propen-α-one* (VIII, R = $CH_3$), as an intermediate. This compound was readily prepared from 4-methoxy-2-methylacetophenone and 4-methoxy-2-methylbenzaldehyde. However, treatment of (VIII, R = $CH_3$) with hydrogen peroxide led, not to the expected 2 : 3-epoxy-derivative, but to an unstable compound, possibly *αγ-di-(4-methoxy-2-methylphenyl)propendiolone* (IX), which oxidised spontaneously to 4-methoxy-2-methylbenzoic acid. Had the epoxy-compound been obtained, it should have been possible to proceed to 2 : 2′-dimethyldeoxyanisoin by the general method of W. Baker and Robinson (*J.*, 1932, 1798).

It is hoped to describe experiments leading to the synthesis of one or more of the remaining stilboestrol analogues (II, IV, V, and VI) in a later communication.

Biological assay of compound (III) and its dibenzyl analogue, carried out by Dr. G. Brownlee and Mr. A. F. Green at the Wellcome Physiological Research Laboratories, Beckenham, has shown that both these compounds possess considerable oestrogenic activity. Detailed results will be published elsewhere.

## Experimental.

Melting points are uncorrected.

Pure 4-methoxy-2-methylbenzaldehyde was prepared in good yield by methylation of 4-hydroxy-2-methylbenzaldehyde (Gattermann and Berchelmann, *Ber.*, 1898, **31**, 1767), as described by Simonsen (*J.*, 1918, 777) for 2-methoxy-3-methylbenzaldehyde. Treatment of 4-methoxy-2-methylbenzaldehyde (14·0 g.) in ethanol (20 ml.) with potassium cyanide (5·1 g.) in water (17 ml.) yielded mainly unchanged aldehyde, b. p. 135—137°/15 mm., and a residual gum, from which a small quantity of pale yellow needles, m. p. 134—135°, was isolated by crystallisation from methanol. This substance appeared to be 2 : 2′-*dimethylanisil* (Found: C, 72·7; H, 6·0. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·1%).

*α-(4-Methoxyphenyl)-γ-(4′-methoxy-2′-methylphenyl)propen-α-one* (VIII, R = H).—A solution of *p*-methoxyacetophenone (10·4 g.) in 4-methoxy-2-methylbenzaldehyde (10·4 g.) was treated with a solution of sodium (1·6 g.) in methanol (80 ml.). After 12 hours, the crystalline precipitate was collected and washed with methanol and water. The *ketone* crystallised from methanol in pale yellow needles, m. p. 126—127° (16·4 g.) (Found: C, 76·8; H, 6·5. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%).

*αγ-Di-(4-methoxy-2-methylphenyl)propen-α-one* (VIII, R = Me) was prepared in a similar manner by treating a solution of 4-methoxy-2-methylbenzaldehyde (12·8 g.) and 4-methoxy-2-methylacetophenone (Eijkman, *Chem. Weekblad*, 1904, **1**, 453) (13·8 g.) in methanol (35 ml.) with a solution of sodium (2·0 g.) in methanol (65 ml.). It crystallised in yellow plates (19·5 g.), m. p. 74—76° (Found: C, 77·2; H, 6·9. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

*Oxidation of the Chalkone* (VIII, R = Me) *with Hydrogen Peroxide.*—Hydrogen peroxide (15%, 13 ml.) was added to a solution of the chalkone (12·7 g.) in warm methanol (150 ml.), followed gradually by 2N-sodium hydroxide (11 ml.). The resulting oil, on extraction with ether in the usual way, was isolated as a pale yellow gum, which could not be crystallised. The gum was refluxed for 2 hours with ethanol (200 ml.) and 30% aqueous sodium hydroxide (25 ml.) and the solution poured into water and acidified. The ethereal extract, on evaporation, yielded an oil which crystallised from methanol or aqueous acetic acid to give stout yellow prisms (7·0 g.), m. p. 114—116°; this compound may have been *αγ-di-(4-methoxy-2-methylphenyl)propendiolone* (IX) (Found: C, 69·5; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%). On standing in air, it oxidised to a white powder, which crystallised from acetic acid in needles, m. p. 175—176°, identical with 4-methoxy-2-methylbenzoic acid.

*2-Phenyl-4-(4′-methoxy-2′-methylbenzylidene)-5-oxazolone.*—4-Methoxy-2-methylbenzaldehyde (100·7 g.), hippuric acid (120 g.), powdered fused sodium acetate (56 g.) and acetic anhydride (171 g.) were heated together at 100° for 4 hours with occasional shaking. The crystalline condensation product was collected and washed first with methanol (*ca.* 600 ml.) and then with boiling water (2 l.). A sample of the resulting *oxazolone* (136 g.) crystallised from ethyl acetate–ethanol in bright yellow needles, m. p. 144° (Found: C, 73·6; H, 5·0. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1%).

*Methyl 4-Methoxy-2-methylphenylacetate.*—The oxazolone (136 g.) was refluxed with 10% sodium hydroxide solution

(1000 ml.) for 6 hours. The filtered solution was well stirred and treated at 0° with hydrogen peroxide (28%, 100 ml.), which was slowly added over ½ hour. After two hours, the liquid was acidified with concentrated hydrochloric acid and extracted with ether. The dried ethereal extract, on evaporation, afforded a mixture of benzoic and 4-methoxy-2-methylphenylacetic acids. This mixture was treated with methanol (800 ml.) and concentrated sulphuric acid (20 ml.) and refluxed for 3 hours. Half the methanol was removed, the residue poured into water (1 l.) and the ethereal extract washed with dilute sodium carbonate solution and dried. Fractionation of this extract gave methyl benzoate (44 g.), b. p. 77—90°/10 mm., and methyl 4-methoxy-2-methylphenylacetate (55·3 g.), b. p. 147—149°/10 mm., as an odourless, strongly refracting oil.

*4-Methoxy-2-methylphenylacetic Acid* (VII).—The methyl ester (55·3 g.), potassium hydroxide (40 g.), water (80 ml.) and methanol (300 ml.) were refluxed for 3 hours and the residue, after removal of most of the methanol, diluted with water and acidified. The resulting precipitate, crystallised from water (1 l.) containing enough acetic acid to yield a homogeneous solution at the boiling point, gave *4-methoxy-2-methylphenylacetic acid* in glistening leaflets (44·9 g.), m. p. 104—106° (Found: C, 66·6; H, 6·7. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%). The acid (VII) (44·9 g.) with thionyl chloride (60 g.) was refluxed for 1 hour; on distillation the acid chloride (42·5 g.) was obtained as a colourless liquid with a pleasant aromatic odour, b. p. 147—149°/12 mm. On treatment with ammonia, the acid chloride gave *4-methoxy-2-methylphenylacetamide*, which crystallised from water in stout needles, m. p. 162—163° (Found: N, 8·0. $C_{10}H_{13}O_2N$ requires N, 7·8%).

*2 : 2′-Dimethyldeoxyanisoin.*—Powdered aluminium chloride (30·5 g.) was added to a mixture of *m*-methylanisole (37 g.) and dry carbon disulphide (300 ml.) at 0°. The temperature was then reduced to −10° and 4-methoxy-2-methylphenylacetyl chloride (30 g.) was slowly added with stirring over 15 minutes; stirring was continued for 1—2 hours and then the mixture was refluxed for 1 hour, decomposed with ice and hydrochloric acid and the volatile products removed by steam-distillation. The residual oil and water mixture was shaken with ether (250 ml.), and the solid that had separated during 12 hours was collected and crystallised twice from methanol to give colourless prisms of *2 : 2′-dimethyldeoxyanisoin* (12·8 g.), m. p. 93—94° (Found: C, 76·1; H, 7·2. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·1%). A further 3·5 g., m. p. 91—92°, was obtained from the mother-liquors and from the original ether extract.

*αβ-Di-(4-methoxy-2-methylphenyl)propan-α-one.*—2 : 2′-Dimethyldeoxyanisoin (12·1 g.) was added to a solution of sodium (3·3 g.) in ethanol (90 ml.) and the whole boiled for 15 minutes giving an orange solution. Methyl iodide (45 g.) was gradually added to the cooled solution and the mixture refluxed for 16 hours. The residue, after removal of methyl iodide and ethanol, was treated with water and extracted with ether; a quantity of starting material (*ca.* 5 g.) then separated. After 12 hours, the latter was removed and the ethereal layer dried and distilled. The oily distillate, after several days at 0° in 3 volumes of ether, deposited a further 0·9 g. of starting material, which was also removed. Fractionation of the filtrate gave the ketone as an oil (5·5 g.), b. p. 202—203°/1 mm.

*4 : 4′-Dimethoxy-α : β : 2 : 2′-tetramethylstilbene.*—A solution of the above ketone (4·5 g.) in dry ether was added to the Grignard reagent prepared from magnesium (0·55 g.) and methyl iodide (4·5 g.) in ether. After several hours, the product was decomposed with acid and worked up in the usual way by extraction with ether. The resulting oil recrystallised from hexane (A) in soft plates (2·8 g.), m. p. 91—98°, probably consisting of impure *βγ*-di-(4-methoxy-2-methylphenyl)-butan-*γ*-ol, which was converted to the stilbene derivative without further purification. The carbinol (2·8 g.) was dissolved in a saturated solution of hydrochloric acid in glacial acetic acid (12 ml.), allowed to stand for 24 hours, and then poured into water. The ethereal extract was well washed with sodium carbonate solution, dried, and fractionated to give an oil (2·0 g.), b. p. 172—173°/1—2 mm., which on crystallisation from methanol (B) yielded *4 : 4′-dimethoxy-α : β : 2 : 2′-tetramethylstilbene* (0·75 g.), as prisms, m. p. 97—98° (Found: C, 80·9; H, 8·3. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·1%). A further crop (0·7 g.) was obtained from the hexane mother liquor (A) of the carbinol (see above). A crude oily isomer of the crystalline stilbene was isolated from both mother liquors (A) and (B) by evaporation.

*4 : 4′-Dimethoxy-α : β : 2 : 2′-tetramethyldibenzyl.*—The above oily isomer (1·5 g.) was dissolved in acetic acid (15 ml.) and hydrogenated at room temperature and 2 atm. in the presence of Adams' catalyst. The filtrate, diluted with water (8 ml.), gave crystals of the *dimethoxydibenzyl* derivative, which separated from methanol in long prisms (0·3 g.), m. p. 138—139° (Found: C, 80·5; H, 8·8. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%).

*4 : 4′-Dihydroxy-α : β : 2 : 2′-tetramethyldibenzyl.*—4 : 4′-Dimethoxy-α : β : 2 : 2′-tetramethyldibenzyl (0·23 g.) was boiled for 2 hours with glacial acetic acid (1·5 ml.) and hydriodic acid (*d.* 1·7) (1·0 ml.). The cooled liquid was added to water (20 ml.) and the colour removed by a trace of sodium thiosulphate. The precipitate, on recrystallisation from benzene, afforded the dihydroxydibenzyl derivative in long needles, drying to a white powder (0·14 g.), m. p. 189—190°. The diacetate crystallised from methanol in long prisms, m. p. 161—162° (cf. Bretschneider *et al.*, *loc. cit.*).

*4 : 4′-Dihydroxy-α : β : 2 : 2′-tetramethylstilbene* (III).—Crystalline 4 : 4′-dimethoxy-α : β : 2 : 2′-tetramethylstilbene (0·8 g.) was added to the Grignard reagent prepared from magnesium (0·5 g.) and methyl iodide (1·2 ml.) and the mixture heated at 170° until reaction had ceased (½ hour). The buff powder was decomposed with ice and dilute hydrochloric acid, and the resulting gum extracted with hot benzene (20 ml.). The extract, dried, cleaned with charcoal, and cooled, yielded *4 : 4′-dihydroxy-α : β : 2 : 2′-tetramethylstilbene* (III), which crystallised from benzene in characteristic needles (0·3 g.), m. p. 208—210°, containing solvent of crystallisation. On drying in air they changed into a white amorphous powder (0·3 g.), m. p. 208—210°, with characteristic "electric" properties (Found: C, 80·3; H, 7·8. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%).

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Development Laboratories, Wellcome Chemical Works, Dartford. [*Received, October 10th*, 1945.]

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## 23. *Aminoalkyl Esters of Thiazolecarboxylic and Thiazolyl-4-acetic Acids.*

By E. R. H. Jones, F. A. Robinson, and M. N. Strachan.

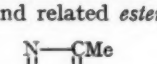
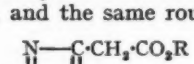
Various alternative routes to the β-diethylaminoethyl ester of 4-methylthiazole-5-carboxylic acid have been investigated. Similar esters of other carboxylic and acetic acids of the thiazole series have been prepared, either by alcoholysis of the ethyl esters or by reaction of the acids with β-chloroethyldiethylamine and potassium carbonate in acetone solution.

Johnson and his co-workers (*J. Amer. Chem. Soc.*, 1929, **51**, 1815; 1930, **52**, 1585, 3724, 4139, 4141; 1931, **53**, 1470, 1475; *Rec. trav. chim.*, 1930, **49**, 1066; 1931, **50**, 72; U.S.Ps. 1,743,083, 1,970,656, 2,014,498, 2,020,650,

2,030,373) were the first to investigate the potentialities of monocyclic thiazoles as chemotherapeutic agents. They were mainly concerned with 2-arylthiazoles but, apart from general statements as to the pharmacological interest or the biological potency of individual or groups of compounds, no detailed pharmacological reports have been published. Similar studies have subsequently been made by other investigators (Niederl *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 707; 1939, **61**, 1145; Adams *et al.*, *ibid.*, 1937, **59**, 2260, 2262; Wetherill and Hann, *ibid.*, 1934, **56**, 970; 1935, **57**, 1752; Rose, Shonle, and Chen, *Pharm. Arch.*, 1940, **11**, 81; Levvy and Nisbet, *J.*, 1938, 1053; U.S.Ps. 2,027,030, 2,242,237; B.P. 549,846) especially with aryl-substituted thiazolines. Erlenmeyer and Meyenburg (*Helv. Chim. Acta*, 1937, **20**, 1389) and Doran and Shonle (*J. Org. Chem.*, 1938, **3**, 193) have synthesised and examined the pharmacological properties of a number of 5 : 5-disubstituted 2 : 4-thiazolidiones (see following paper) and the diethylamides of two thiazolecarboxylic acids have been investigated as analeptics (Erlenmeyer and Meyenburg, *Helv. Chim. Acta*, 1937, **20**, 204; Hoffer and Reinert, *Arch. int. Pharmacodyn.*, 1937, **56**, 211). The incorporation of the thiazole ring system into antibacterial agents of the sulphanilamide series, furnishing substances of considerable clinical value, provides the most familiar example of the utilisation of the thiazole ring system in chemotherapeutic agents. The marked local anæsthetic or spasmolytic properties of the dialkylaminoalkyl esters of aminobenzoic, diphenylacetic, fluorene-9-carboxylic and related acids suggested that the preparation and examination of such derivatives in the thiazole series might yield interesting results.

After considerable activity in the period 1885—1895, the carboxylic acids of the thiazole series received little attention until 1935 when, after the isolation of 4-methylthiazole-5-carboxylic acid (I; R = H) by the degradation of vitamin $B_1$, interest in these compounds was revived. All the thiazolecarboxylic and the thiazolylacetic acids utilised in the research described in this paper were prepared by the classical method, *i.e.*, the condensation of a halogenated α- or β-keto-ester with either thioformamide or thioacetamide.

The moderately easily accessible acid (I; R = H) was smoothly converted into its *β-diethylaminoethyl* (I; R = $CH_2 \cdot CH_2 \cdot NEt_2$) and related *esters via* the *acid chloride*, and the same route could conveniently be

(I.)  (II.) 

employed to prepare the N-*diethylamide* and analogous compounds. This method was not applicable to the other acids studied, because of the difficulty of obtaining the acid chlorides, and various alternative routes to the above β-diethylaminoethyl ester were investigated in order to establish general methods of synthesis. Treatment of the acid with β-chloroethyldiethylamine in acetone solution in the presence of anhydrous potassium carbonate (cf. Miescher and Hoffman, *Helv. Chim. Acta*, 1941, **24**, 458; Hoffman, *ibid.*, 1941, **24**, 36—40E) gave the desired ester in good yield and alcoholysis of the ethyl ester, simply by heating with β-diethylaminoethyl alcohol, proved equally effective. The latter reaction is readily reversible, refluxing the diethylaminoethyl ester with an excess of alcohol furnishing an excellent yield of the ethyl ester.

The fourth route investigated proved less successful but some interesting points emerged from its study. In the first place *β-chloroethyl acetoacetate* was prepared readily from the ethyl ester by refluxing with ethylene chlorohydrin. Bromination of this ester, followed by condensation with thioformamide, gave *β-chloroethyl 4-methylthiazole-5-carboxylate* (I; R = $CH_2 \cdot CH_2Cl$). Treatment of the latter with diethylamine under widely varying conditions only gave small or negligible yields of the required diethylaminoethyl ester, the main product in most cases consisting of *NN'*-tetra-ethyl-1 : 2-diaminoethane ($Et_2N \cdot CH_2 \cdot CH_2 \cdot NEt_2$). Gilman and Pickles (*J. Amer. Chem. Soc.*, 1925, **47**, 251) had had similar experience and had isolated the same compound when attempting to effect reaction between diethylamine and β-chloroethyl benzenesulphonate.

The β-chloroethyldiethylamine method was employed to prepare the *β-diethylaminoethyl ester* of 2 : 4-*dimethylthiazole-5-carboxylic acid* and the alcoholysis route was applied to produce a similar ester from *ethyl 2-methylthiazole-4-carboxylate*. Despite the statement of Steude (*Annalen*, 1891, **261**, 27) and more recently of Erlenmeyer and Heitz (*Helv. Chim. Acta*, 1942, **25**, 832) that the latter ethyl ester cannot be obtained by condensation of ethyl bromopyruvate with thioacetamide, it was found that this reaction could be effected smoothly in alcoholic solution.

*Ethyl thiazolyl-4-acetate* (II; R = Et) was prepared in *ca.* 30% yield from ethyl γ-bromoacetoacetate and thioformamide, and hydrolysis with potassium hydroxide gave the corresponding *acid* (II; R = H). It may be noted here that the employment of potassium rather than sodium hydroxide for the hydrolysis of esters in this series of compounds results in remarkably improved yields of acidic products; in some cases no acid at all could be isolated after hydrolysis with sodium hydroxide. The alcoholysis method furnished excellent yields of the *β-diethylaminoethyl esters* of both *thiazolyl-* and *2-methylthiazolyl-4-acetic acids*.

None of the methods outlined above could be applied successfully to prepare the *diethylaminoethyl ester* of *2-amino-4-methylthiazole-5-carboxylic acid*. It was eventually produced by the following synthesis. Alcoholysis of ethyl acetoacetate with β-diethylaminoethyl alcohol gave a 25% yield of *β-diethylaminoethyl acetoacetate*, and bromination followed by condensation of the brominated product with thiourea yielded the required ester.

All the aminoalkyl esters examined pharmacologically exhibited spasmolytic and analeptic properties, as was to be expected from their resemblance to β-diethylaminoethyl diphenylacetate hydrochloride (Trasentin) and β-diethylaminoethyl 1-*cyclo*hexyl-1-phenylacetate hydrochloride (Trasentin 6H). The neurotropic action

was less marked than the musculotropic action; thus, whereas the ability of various aminoalkyl esters of 4-methylthiazole-5-carboxylic acid (I) to inhibit the contractions produced by acetylcholine was only about one-thousandth that of Trasentin, the effect of the most potent compound, the diethylaminoethyl ester, in relaxing histamine spasm was one-quarter that of Trasentin 6H. The diethylaminoethyl esters of the thiazolylacetic acids exhibited only a fraction of the musculotropic action of the corresponding esters of 4-methylthiazole-5-carboxylic acid and the introduction of the 2-amino group into the latter markedly reduced the activity. The dimethyl- and the diethyl-aminoethyl esters of (I) produced convulsions in doses equal to one-quarter to one-sixth of the dose required with Trasentin 6H, and one-sixth to one-eighth of that required with 1 : 2-pentamethylenetetrazole (Leptazol). Only the diethylaminoethyl ester of (I) was effective in antagonising a lethal dose of a short-acting barbiturate; none of the esters was effective against the long-acting variety. The diethylaminoethyl ester of the amino-acid, which might have been expected to show local anæsthetic properties, was practically devoid of activity. The *N*-diethylamide of (I) and analogous compounds had analeptic properties and caused convulsions, but had no action on the heart comparable with that of *N*-diethylnicotinamide (Nikethamide, Coramine).

## Experimental.

*Derivatives of 4-Methylthiazole-5-carboxylic Acid.*—The condensation of thioformamide with ethyl α-bromoacetoacetate (Kharasch, Sternfield, and Mayo, *J. Amer. Chem. Soc.*, 1937, **59**, 1655) was effected according to Erlenmeyer and Meyenburg (*Helv. Chim. Acta*, 1937, **20**, 204; cf. Harington and Moggridge, *J.*, 1939, 443). The *picrate* of the *ethyl ester* formed yellow prismatic needles from alcohol, m. p. 110° (Found : N, 14·15. $C_{12}H_{12}O_9N_4S$ requires N, 14·0%).

The acid was obtained in practically theoretical yield by heating the ethyl ester (20 g.) on the steam bath with aqueous potassium hydroxide (150 c.c., 10%) for 30 mins. (cf. the 75% yield of Clarke and Gurin, *J. Amer. Chem. Soc.*, 1935, **57**, 1876). The *quinine salt* was prepared by refluxing an alcoholic solution of equimolecular quantities of the acid and base for several hours, evaporating to dryness and crystallising from ethyl acetate. This procedure gave needles, m. p. 189·5° (decomp.) (Found : C, 64·15; H, 6·6. $C_{25}H_{29}O_4N_3S$ requires C, 64·2; H, 6·25%). The acid (22 g.), after being refluxed with thionyl chloride (40 c.c.) for 3 hours, removing the excess of the latter under reduced pressure and subliming the product at 40—55° (bath temp.)/$10^{-4}$ mm., yielded the *acid chloride* (20 g.) in short hexagonal prisms, m. p. 64° (Found : C, 37·3; H, 2·45. $C_5H_4ONClS$ requires C, 37·15; H, 2·5%).

*β-Diethylaminoethyl Ester.*—(*a*) The acid chloride (3 g.) in dry acetone (25 c.c.) was treated with diethylaminoethyl alcohol (2·2 g.) and the mixture refluxed for 6 hours (A). The crystalline solid which separated on cooling was recrystallised from alcohol–acetone giving the *hydrochloride* of the *diethylaminoethyl ester* (75—80% yield) as needles, m. p. 167° (Found : C, 47·6; H, 7·1. $C_{11}H_{19}O_2N_2ClS$ requires C, 47·4; H, 6·85%). When the acetone solution (A) was evaporated and the residue treated with sodium bicarbonate and extracted with ether the *diethylaminoethyl ester* (85% yield) was obtained as a viscous oil, m. p. *ca.* 1—2°, b. p. 80° (bath temp.)/$10^{-4}$ mm., $n_D^{24°}$ 1·5060 (Found : C, 54·75; H, 7·95. $C_{11}H_{18}O_2N_2S$ requires C, 54·5; H, 7·5%). On shaking this water insoluble ester with 2N-sodium hydroxide solution for 5 minutes, practically quantitative yields of 4-methylthiazole-5-carboxylic acid and diethylaminoethyl alcohol were produced. (The *picrate* of *diethylaminoethyl alcohol*, yellow crystals from acetone, has m. p. 79° (Found : N, 15·9. $C_{12}H_{18}O_8N_4$ requires N, 16·2%).) With a deficiency of picric acid the diethylaminoethyl ester gives a *monopicrate* as yellow crystals from acetone, m. p. 132° (Found : N, 14·7. $C_{17}H_{21}O_9N_5S$ requires N, 14·85%), and with an excess of the reagent a *dipicrate* is formed. This can also be obtained from the monopicrate. It separates as yellow crystals from acetone, m. p. 125—126° (Found : N, 15·7. $C_{23}H_{24}O_{16}N_8S$ requires N, 16·0%). The *methiodide* of the ester, obtained after standing for some days at 20° with an excess of the reagent, formed hexagonal leaflets from acetone–alcohol, m. p. 195° (Found : N, 7·15. $C_{12}H_{21}O_2N_2IS$ requires N, 7·3%).

(*b*) A mixture of 4-methylthiazole-5-carboxylic acid (3 g.), anhydrous potassium carbonate (2 g.) and β-chloroethyldiethylamine (4·3 g., 1·5 mol.) in acetone (100 c.c.) was refluxed for 4 hours. The mixture was filtered, the filtrate evaporated and the residue distilled, giving the diethylaminoethyl ester (2·9 g., 60%), m. p. 3°, b. p. 162—163°/12 mm., $n_D^{19°}$ 1·5106, which formed the same dipicrate, m. p. 126° (mixed m. p.), and gave the same hydrolysis products as the sample prepared by method (*a*).

(*c*) A solution of ethyl 4-methylthiazole-5-carboxylate (2·6 g.) in diethylaminoethyl alcohol (8 g., 4 mols.) was heated for 20 hours at 170—175° using a short reflux condenser through which the ethyl alcohol produced could be eliminated. Distillation gave the diethylaminoethyl ester (2·5 g., 70%), b. p. 165—166°/15 mm., $n_D^{13·5°}$ 1·5102 (dipicrate). Neither increasing the time of reaction nor the proportion of the diethylaminoethyl alcohol employed caused any increase in yield. On heating the ester (1·9 g.) with alcohol (40 c.c.) under reflux for 6½ hours, diethylaminoethyl alcohol (0·5 g., 55%), b. p. *ca.* 60°/15 mm., $n_D^{21°}$ 1·4413, and ethyl 4-methylthiazole-5-carboxylate (1·2 g., 90%), b. p. 110—115°/15 mm., $n_D^{21°}$ 1·5058 (picrate), were obtained on distillation.

*β-Dimethylaminoethyl Ester Hydrochloride.*—Prepared in 80% yield according to method (*a*) above, from dimethylaminoethyl alcohol, it formed prisms from alcohol–acetone, m. p. 202° (Found : C, 42·9; H, 5·75. $C_9H_{18}O_2N_2ClS$ requires C, 43·1; H, 6·05%).

*β-Piperidinoethyl Ester Hydrochloride.*—Method (*a*) employing β-piperidinoethyl alcohol (Blicke and Maxwell, *J. Amer. Chem. Soc.*, 1942, **64**, 429) gave a 65% yield of silky needles, from alcohol–acetone, m. p. 190° (decomp.) (Found : C, 49·95; H, 6·4. $C_{12}H_{19}O_2N_2ClS$ requires C, 49·55; H, 6·6%).

*β-Morpholinoethyl Ester Hydrochloride.*—Prepared by route (*a*) in 85% yield. The crystals from alcohol have m. p. 207° (decomp.) (Found : C, 45·35; H, 6·05. $C_{11}H_{17}O_3N_2ClS$ requires C, 45·1; H, 5·85%).

*β-Diethylaminopropyl Ester Hydrochloride.*—The alcohol was prepared from propylene oxide and diethylamine according to Goldfarb (*J. Amer. Chem. Soc.*, 1941, **63**, 2280) except that little reaction appeared to ensue with completely anhydrous reagents. After adding a little water a smooth reaction occurred giving a 75% yield of the alcohol. The ester hydrochloride, prepared by (*a*) above in 75% yield, formed needles from alcohol–ligroin (b. p. 60—80°), m. p. 156·5° (Found : C, 49·5; H, 7·55. $C_{12}H_{21}O_2N_2ClS$ requires C, 49·2; H, 7·25%).

*γ-Diethylaminopropyl Ester Hydrochloride.*—The method of Hromatka (*Ber.*, 1942, **75**, 136) for the amino-alcohol was found unsatisfactory and that due to Campbell and Campbell (*Proc. Indiana Acad. Sci.*, 1939, **49**, 101) was employed. Using method (*a*) and crystallising first from alcohol–acetone and then from alcohol–ligroin (b. p. 60—80°) the hydrochloride was obtained in 40% yield in needles, m. p. 153° (Found : C, 49·15; H, 7·05. $C_{12}H_{21}O_2N_2ClS$ requires C, 49·2; H, 7·25%).

*β-Chloroethyl Ester.*—A solution of thioformamide (9·3 g.) in alcohol (20 c.c.) was cooled to 8° and the α-bromocompound (30·8 g.) from β-chloroethyl acetoacetate (see below, for preparation) in alcohol (10 c.c.) was added over 7 mins. with stirring and cooling, the temperature being allowed to rise only to 30°. After standing overnight and diluting with water (200 c.c.), concentrated hydrochloric acid (50 c.c.) was added, non-basic material was removed with ether and,

after addition of excess solid sodium bicarbonate, isolation with ether gave the ester (6 g., 25%), b. p. 150—160°/20 mm., as a yellow oil which solidified on keeping. Recrystallisation from ligroin (b. p. 40—60°) gave needles, m. p. 59° (Found : C, 40·85; H, 4·05. $C_7H_8O_2NClS$ requires C, 40·9; H, 3·9%). Hydrolysis with 10% aqueous potassium hydroxide gave 4-methylthiazole-5-carboxylic acid (quinine salt, m. p. and mixed m. p.). The *picrate* crystallised from alcohol in yellow plates, m. p. 115° (Found : N, 12·85. $C_{13}H_{11}O_9N_4ClS$ requires N, 12·9%). Attempts to convert the above ester into the diethylaminoethyl ester were unsuccessful, except when the chloro-ester was made into the iodo-ester and the latter was heated in a sealed tube at 130° with a large excess of diethylamine. In most of the numerous experiments carried out, *NN'*-tetraethyl-1 : 2-diaminoethane, b. p. 78—80°/20 mm., $n_D^{20°}$ 1·4366 (Found : N, 16·15. Calc. for $C_{10}H_{24}N_2$ : N, 16·25%), was obtained in varying amounts. Its dihydrochloride had m. p. 190—191° (Gilman and Pickles, *J. Amer. Chem. Soc.*, 1925, **47**, 251, give b. p. 70—72°/10 mm. for the base and m. p. 187° for the dihydrochloride). The *dipicrate* crystallised from acetone in yellow plates, decomp. at 243° (Found : C, 41·95; H, 4·95. $C_{32}H_{30}O_{14}N_8$ requires C, 41·9; H, 4·8%).

*Diethylamide.*—(*a*) (cf. method of Erlenmeyer and Meyenburg, *loc. cit.*). A mixture of the acid chloride (3 g.) and diethylamine hydrochloride (2·1 g.) was heated for 2 hours at 160°, occasionally returning the sublimate to the melt. The residue was treated with sodium hydroxide solution and isolation with ether gave the *diethylamide* (2·2 g., 60%) as a pale yellow oil, completely miscible with water, b. p. 287° (slight decomp.), 169—170°/23 mm., 85—90° (bath temp.)/$10^{-4}$ mm., $n_D^{22°}$ 1·5240 (Found : C, 54·0; H, 7·25. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1%). The *picrate* formed yellow crystals from acetone, m. p. 118° (Found : N, 16·15. $C_{15}H_{17}O_8N_5S$ requires N, 16·4%).

(*b*) The acid chloride (10 g.) and diethylamine (9·8 g.) were mixed in cold ether (300 c.c.). After 5 mins. the diethylamine hydrochloride was separated and evaporation and distillation of the residue gave the diethylamide (10·3 g., 85%), having constants as above.

*Dimethylamide.*—Method (*a*) gave only a 15% yield, but a 90% yield was obtained by method (*b*). It is a water-soluble mobile oil, b. p. 164°/23 mm., 80—85° (bath temp.)/$10^{-4}$ mm., $n_D^{22°}$ 1·5460 (Found : C, 49·85; H, 6·1. $C_7H_{10}ON_2S$ requires C, 49·4; H, 5·9%). The *picrate* formed yellow crystals, m. p. 109°, from acetone (Found : N, 17·5. $C_{13}H_{13}O_8N_5S$ requires N, 17·55%).

*Piperidino-amide.*—Method (*a*) failed to give more than a 15% yield but method (*b*) gave an 80% yield of amide with b. p. 197°/23 mm., 90° (bath temp.)/$10^{-4}$ mm., $n_D^{21°}$ 1·5634 (Found : C, 57·5; H, 6·8. $C_{10}H_{14}ON_2S$ requires C, 57·1; H, 6·7%). The *picrate* crystallised from alcohol in yellow needles, m. p. 148·5° (Found : N, 15·7. $C_{16}H_{17}O_8N_5S$ requires N, 15·95%).

*Morpholino-amide.*—Prepared in 75% yield by method (*b*) this had b. p. 206°/23 mm., 100° (bath temp.)/$10^{-4}$ mm., $n_D^{21°}$ 1·5649. It gradually solidified on keeping and after crystallisation from ligroin (b. p. 80—100°) it was obtained in prisms, m. p. 54—55° (Found : C, 51·3; H, 5·45. $C_9H_{12}O_2N_2S$ requires C, 50·95; H, 5·7%). It is highly hygroscopic. The *picrate* crystallised from acetone, m. p. 181·5° (slight decomp.) (Found : N, 16·0. $C_{15}H_{16}O_9N_5S$ requires N, 15·85%).

*Derivatives of* 2 : 4-*Dimethylthiazole-5-carboxylic Acid.*—*β-Diethylaminoethyl ester.* The acid (12 g.; Erlenmeyer *et al.*, *Helv. Chim. Acta*, 1938, **21**, 1020) was treated with β-chloroethyldiethylamine (13 g.) and anhydrous potassium carbonate (6 g.) in dry acetone (400 c.c.) as described above. The *ester* (15·3 g., 80%) had b. p. 121—124°/3 mm., $n_D^{21°}$ 1·5071 (Found : C, 56·25; H, 7·85. $C_{12}H_{20}O_2N_2S$ requires C, 56·25; H, 7·85%). Hydrolysis of the ester by refluxing for 30 mins. with 10% aqueous potassium hydroxide gave a 65% yield of the parent acid, m. p. 233°, undepressed on admixture with an authentic specimen. The *dipicrate* of the *diethylaminoethyl ester* formed fine yellow needles, m. p. 163°, on crystallisation from acetone (Found : N, 15·45. $C_{24}H_{26}O_{16}N_8S$ requires N, 15·7%). The *amide*, prepared from the ethyl ester by treatment with 0·880 ammonia, crystallised from alcohol–ligroin (b. p. 60—80°) as plates or needles, m. p. 140° (Found : N, 17·55. $C_6H_8ON_2S$ requires N, 17·95%).

*Derivatives of* 2-*Methylthiazole-4-carboxylic Acid.*—When a solution of thioacetamide (4 g., 1·3 mol.) in alcohol (25 c.c.) was treated with ethyl bromopyruvate (7·8 g.; Ward, *J.*, 1923, 2210; Steude, *Annalen*, 1891, **261**, 25) a yellow colour developed rapidly and the temperature of the reaction mixture rose to 60°. After standing overnight at 20° 2N-hydrochloric acid was added and the solution was extracted with ether to remove non-basic material. Isolation of the product with ether after treatment with an excess of bicarbonate gave *ethyl 2-methylthiazole-4-carboxylate* (5 g., 75%) which sublimed at about 70° (bath temp.)/$10^{-4}$ mm. Crystallisation from ligroin (b. p. 60—80°) gave prismatic needles, m. p. 58° (Found : C, 49·0; H, 5·35. $C_7H_9O_2NS$ requires C, 49·1; H, 5·3%). With methyl alcohol as solvent for the condensation, poorer yields (60%) were obtained and on using chloroform as solvent the hydrobromide (m. p. *ca.* 120°) of a water-soluble base (m. p. 74°), which could not be investigated further, was obtained. Reaction of the ester with hydrogen chloride or picric acid gave only intractable gums, but the *amide* was obtained with 0·880 ammonia. After crystallisation from alcohol–ligroin (b. p. 60—80°) it had m. p. 152° (Found : N, 19·5. $C_5H_6ON_2S$ requires N, 19·7%).

The ethyl ester (10 g.) in diethylaminoethyl alcohol (40 g.) was refluxed gently for 36 hours in a flask fitted with a short air condenser. Fractionation of the residual liquid gave the water-soluble *β-diethylaminoethyl ester* (9·9 g., 70%), b. p. 140°/3·5 mm., $n_D^{19°}$ 1·5170 (Found : C, 54·15; H, 8·05. $C_{11}H_{18}O_2N_2S$ requires C, 54·5; H, 7·5%). The *monopicrate* was crystallised from aqueous acetone and had m. p. 74—76° (after sintering at *ca.* 70°) (Found : N, 14·85. $C_{17}H_{21}O_9N_5S$ requires N, 14·85%).

*Derivatives of Thiazolyl-4-acetic Acid.*—Many attempts to prepare the ester gave unsatisfactory yields. The following is a description of the procedure which gave the best results. Ethyl γ-bromoacetoacetate (28·7 g.; Conrad and Schmidt, *Ber.*, 1896, **29**, 1043) in alcohol (50 c.c.) was treated with a solution of thioformamide (11 g.) in alcohol (15 c.c.), the latter being added in small portions with stirring so that the temperature did not rise above 40°. After the addition, the mixture was heated under reflux for 15 minutes when ammonium bromide (6—7 g.) separated. Following extensive dilution with 2N-hydrochloric acid and ether extraction, the aqueous portion was mixed with excess of sodium bicarbonate and isolation with ether followed by fractionation gave the *ethyl ester* (5·6 g., 25%), b. p. 122°/15 mm., $n_D^{17°}$ 1·5115 (Found : C, 48·65; H, 5·2. $C_7H_9O_2NS$ requires C, 49·1; H, 5·3%). The *picrate* separated from alcohol in silky yellow needles, m. p. 112° (Found : N, 13·7. $C_{13}H_{12}O_9N_4S$ requires N, 14·0%).

The ester (3·4 g.) was hydrolysed almost immediately on shaking with 10% aqueous potassium hydroxide (20 c.c.) giving *thiazolyl-4-acetic acid* (2 g.), in long needles from benzene, m. p. 139° (Found : C, 42·1; H, 3·6. $C_5H_5O_2NS$ requires C, 41·95; H, 3·5%). It sublimes unchanged at 60—75° (bath temp.)/$10^{-4}$ mm. With thionyl chloride it develops a blue colouration, changing to bluish-red. Light absorption in alcohol : Maximum, 2400A., ε = 3500. The *amide* (75% yield), prepared from the ester with 0·880 ammonia, crystallised from alcohol–ligroin (b. p. 60—80°) in plates, m. p. 124° (Found : N, 19·45. $C_5H_6ON_2S$ requires N, 19·7%).

A solution of ethyl thiazolyl-4-acetate (8·6 g.) in diethylaminoethyl alcohol (15 g., 2·5 mols.) was refluxed for 24 hours in a flask fitted with a short air condenser. Distillation then gave the *β-diethylaminoethyl ester* (11·1 g., 90%), as a pale yellow water-soluble oil, b. p. 186°/29 mm., 80—90° (bath temp.)/$10^{-4}$ mm., $n_D^{21°}$ 1·5048 (Found : C, 54·5; H, 7·65. $C_{11}H_{18}O_2N_2S$ requires C, 54·5; H, 7·5%). The *dipicrate* crystallised from ethyl acetate or chloroform–acetone and had m. p. 102° (Found : N, 15·95. $C_{23}H_{24}O_{16}N_8S$ requires N, 16·0%). On hydrolysis of the ester with 10% aqueous potassium hydroxide, thiazolyl-4-acetic acid (m. p. and mixed m. p.) was obtained.

*Derivatives of* 2-*Methylthiazolyl-4-acetic Acid.*—The following procedure represents an improvement upon the method

of Steude (*Annalen*, 1891, **261**, 40). Ethyl γ-bromoacetoacetate (9 g., distilled) was dissolved in alcohol and thioacetamide (3·2 g.) was added with gentle stirring. Some heat was evolved and after a few minutes a clear yellow solution was obtained. This was allowed to remain undisturbed for some 16 hours. Six such reaction mixtures were mixed together, treated with 2N-hydrochloric acid (500 c.c.) and extracted with ether. The aqueous portion was mixed with excess sodium bicarbonate and isolation by means of ether gave the ethyl ester (35 g., 75%), b. p. 127°/13 mm., $n_D^{21°}$ 1·5020. The *picrate* crystallises from either alcohol or acetone as needles, m. p. 98° or 105°, independent of the solvent employed (Found: N, 13·75. $C_{14}H_{14}O_9N_4S$ requires N, 13·55%). Hydrolysis with aqueous potassium hydroxide gave the acid (60—80% yield), which separated from water or benzene as thick needles, m. p. 124° (Steude, *loc. cit.*, gives m. p. 121°). It sublimed unchanged at 85—95° (bath temp.)/$10^{-4}$ mm. Light absorption in alcohol: Maximum, 2420A., ε = 4500. The *amide*, prepared from ester with 0·880 ammonia, formed plates or needles, m. p. 141°, from alcohol–ligroin (b. p. 60° 80°) (Found: N, 18·2. $C_6H_8ON_2S$ requires N, 17·95%).

*β-Diethylaminoethyl Ester.*—(*a*) The acid (10·7 g.) was refluxed with β-chloroethyldiethylamine (15 g., 1·5 mol.) and anhydrous potassium carbonate (20 g.) in dry acetone (200 c.c.) for 4 hours. This gave the *β-diethylaminoethyl ester* (12 g., 70%), b. p. 131°/4 mm., 70—80° (bath temp.)/$10^{-4}$ mm., $n_D^{19°}$ 1·5001 (Found: C, 56·3; H, 8·1. $C_{12}H_{20}O_2N_2S$ requires C, 56·25; H, 7·85%). The *dipicrate*, crystallised from acetone, had m. p. 126° (Found: C, 40·4; H, 3·8. $C_{24}H_{26}O_{16}N_8S$ requires C, 40·35; H, 3·65%).

(*b*) The ethyl ester (5·5 g.) and β-diethylaminoethyl alcohol (10 g.) were refluxed gently for 32 hours in a flask fitted with a short air condenser. This gave the diethylaminoethyl ester (4 g.; 55%), b. p. 184—185°/22 mm., $n_D^{17°}$ 1·5029 (dipicrate). Hydrolysis of either sample of ester gave β-diethylaminoethyl alcohol (picrate) and the thiazolylacetic acid (m. p. and mixed m. p.).

*β-Chloroethyl Ester.*—Bromine (15·05 c.c.) was added during 30 minutes to a solution of β-chloroethyl acetoacetate (49·4 g.; for preparation, see below) in carbon disulphide (58 c.c.) and chloroform (20 c.c.). After standing overnight, the solution was washed several times with water, dried and evaporated at 50—55°/20 mm. to give the crude γ-bromo-compound (61·3 g., 85%) as a pale brown liquid. Five portions (10·5 g. each) of this product were each treated with thioacetamide (3·25 g.) as for the ethyl ester preparation already described. Fractionation of the crude product gave the *β-chloroethyl ester* (23·5 g., 50%), b. p. *ca.* 170°/20 mm., 110°/4 mm., $n_D^{18°}$ 1·5266 (Found: C, 43·75; H, 4·8. $C_8H_{10}O_2NClS$ requires C, 43·75; H, 4·6%). Hydrolysis with 10% aqueous potassium hydroxide was very rapid at 20° and gave the 2-methylthiazolyl-4-acetic acid (m. p. and mixed m. p.). The *picrate* crystallised from aqueous alcohol in yellow needles, m. p. 103—104° (Found: C, 37·7; H, 3·25. $C_{14}H_{13}O_9N_4ClS$ requires C, 37·45; H, 2·9%).

*Derivatives of 2-Amino-4-methylthiazole-5-carboxylic Acid.*—*β-Diethylaminoethyl ester.* A mixture of β-diethylaminoethyl acetoacetate (24 g.; $n_D^{19°}$ 1·4489; for preparation, see below) and water (125 c.c.) and 2N-hydrochloric acid (75 c.c.) was stirred and cooled (ice) while bromine (19·2 c.c.) was added during 20 minutes. After stirring at 0° for a further 2 hours, treatment with potassium acetate (24 g.) in water (24 c.c.) was followed by the addition of a suspension of thiourea (10 g.) in water (25 c.c.). The solution was stirred during some 16 hours at 20°, filtered, extracted with ether and then made alkaline with ammonia solution. Isolation with ether and purification by crystallisation from alcohol–ligroin (b. p. 60—80°) and sublimation at 110—120° (bath temp.)/$10^{-4}$ mm., gave the *β-diethylaminoethyl ester* (5·5 g., 20%) as glistening plates, m. p. 121° (Found: C, 51·5; H, 7·3. $C_{11}H_{19}O_2N_3S$ requires C, 51·35; H, 7·45%).

*β-Chloroethyl ester.* The α-bromo-compound (62 g.) from β-chloroethyl acetoacetate was added with shaking to an ice-cold solution of thiourea (22 g.) in water (300 c.c.). A precipitate of the hydrobromide was obtained after some hours. A small portion of this, on crystallisation from alcohol–ligroin (b. p. 60—80°), gave the *hydrobromide* of the *β-chloroethyl ester*, m. p. 210° (decomp.) (Found: N, 9·4. $C_7H_{10}O_2N_2ClBrS$ requires N, 9·3%). The reaction mixture was warmed with an equal volume of water to dissolve the hydrobromide, filtered to remove a small residue, and then basified with ammonia solution. The precipitate was crystallised from aqueous alcohol giving the *β-chloroethyl ester* (54 g.; 95%) as fine needles, m. p. 164—165° (Found: C, 38·4; H, 4·1. $C_7H_9O_3N_2ClS$ requires C, 38·1; H, 4·1%).

*Preparation of Intermediates.*—*β-Chloroethyl acetoacetate.* Ethyl acetoacetate (130 g.) was refluxed gently with ethylene chlorohydrin (80·5 g.) in a flask fitted with an air condenser, so arranged that the ethyl alcohol produced escaped from the condenser. After 3—4 hours the liquid temperature had risen from 140° to 195°. Fractionation of the product gave *β-chloroethyl acetoacetate* (84 g., 45%) as a mobile liquid, b. p. 120—121°/19 mm., $n_D^{17°}$ 1·4542 (Found: Cl, 21·6. $C_6H_9O_3Cl$ requires Cl, 21·55%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in deep yellow needles, m. p. 100° (Found: N, 16·55. $C_{12}H_{13}O_6N_4Cl$ requires N, 16·25%). α-Bromination of this ester was effected in the same manner as for the ethyl ester (Kharasch, Sternfield, and Mayo, *J. Amer. Chem. Soc.*, 1937, **59**, 1655) and the crude product, obtained in 80% yield, had $n_D^{18°}$ 1·4919.

*β-Diethylaminoethyl acetoacetate.* A mixture of ethyl acetoacetate (39 g.) and β-diethylaminoethyl alcohol (35 g.) was refluxed for 5—6 hrs. in such a manner that the alcohol formed escaped from the system. Careful fractionation gave the *β-diethylaminoethyl ester* (15 g., 25%) as a pale yellow oil, b. p. 83°/5 mm., $n_D^{18°}$ 1·4481 (Found: N, 7·35. $C_{10}H_{19}O_3N$ requires N, 6·95%). The ester was miscible with water. The *picrate* crystallised from alcohol–ethyl acetate in yellow leaflets, m. p. 70° (Found: N, 13·05. $C_{16}H_{22}O_{10}N_4$ requires N, 13·0%).

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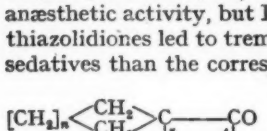
## 24. *Some* 5-spiro*Thiazolidiones.*

By E. R. H. Jones, F. A. Robinson, and M. N. Strachan.

Syntheses *via* the 2-*imino-compounds*, of 5-spirocyclo*pentyl*- and 5-spirocyclo*hexyl*-2 : 4-*thiazolidiones*, of possible interest as hypnotics, are described.

5 : 5-Dialkyl-2 : 4-thiazolidiones, analogous to the well-known barbituric acid derivatives, were synthesised and examined pharmacologically by Erlenmeyer and Meyenburg (*Helv. Chim. Acta*, 1937, **20**, 1389; 1938, **21**, 1013) and Doran and Shonle (*J. Org. Chem.*, 1938, **3**, 193). The classical preparative method, consisting of condensation of an α-halogenated acid or acid derivative with thiourea followed by acid hydrolysis of the resulting imino-compound, was employed in all cases (see also B.P. 503,478; U.S.P. 2,225,903; G.Ps. 670,684,

672,972; F.P. 827,150). The authors reported that the compounds examined exhibited marked sedative and anæsthetic activity, but Doran and Shonle (*loc. cit.*) found that intravenous injection of the sodium salts of the thiazolidiones led to tremors or convulsions and they concluded that members of this series are less satisfactory sedatives than the corresponding barbituric acids.



(I.)

In the hope of effecting appreciable modification of the physiological properties, spiro*thiazolidiones* of type (I) have now been synthesised by conventional methods which require no comment. The light absorption properties of these compounds and of their *N*-methyl ethers, determined in alcohol, are practically identical with those of 2 : 4-thiazolidione (Max. 2250A.; $\varepsilon = 5000$) and of its *N*-methyl ether (Max. 2265A.; $\varepsilon = 4500$).

The only one of these compounds to be tested adequately was 5-*spirocyclo*hexyl-2 : 4-thiazolidione (I; $n = 3$). A solution in dilute alkali when injected into mice produced narcosis and analgesia. The narcotic effect was of shorter duration than that obtained with ethyl*iso*amylbarbituric acid (Amytal) and the analgesic effect was less marked than with morphine. The *N*-methyl ethers were not sufficiently soluble in water to be tested in solution, but *N*-methyl-5-*spirocyclo*hexyl-2 : 4-thiazolidione produced narcosis when injected intraperitoneally in the liquid state. Attempts to induce sleep by rectal administration of the two diones and their *N*-methyl ethers dissolved in equal volumes of *tert.*-amyl alcohol were only partially successful.

## Experimental.

(Light absorption data were determined in alcohol.)

1-*Bromo*cyclo*pentane*-1-*carboxylic Acid*.—A mixture of *cyclo*pentane-carboxylic acid (52 g.; method of Gilman and Kirby, *Org. Syntheses*, Coll. Vol. I (2nd Ed.), 361) and red phosphorus (0·5 g.) was heated on the steam-bath, bromine (160 g.) was added during 2 hours and heating was continued for a further 7 hours. After some hours the excess of bromine was removed by heating under reduced pressure and a pale brown crystalline mass of crude acid (70 g.) was obtained on cooling. A portion was sublimed at 100° (bath temp.)/$10^{-4}$ mm. and on crystallisation from ligroin (b. p. 40—60°) gave 1-*bromo*cyclo*pentane*-1-*carboxylic acid* as leaflets, m. p. 70° (Found: C, 37·55; H, 4·9. $C_6H_9O_2Br$ requires C, 37·35; H, 4·7%). The *anilide*, prepared *via* the acid chloride, formed needles from aqueous alcohol, m. p. 89° (Found: C, 53·9; H, 5·35. $C_{12}H_{14}ONBr$ requires C, 53·75; H, 5·25%).

5-spirocyclo*Pentyl*-2-*imino*-4-*thiazolidone*.—A mixture of thiourea (18 g., 1·5 mol.), anhydrous sodium acetate (20 g.), the crude bromo-acid (30 g.) described above, and dioxan (350 c.c.) was refluxed for 8—9 hours. After filtering, the hot solution was evaporated and the residue was treated with saturated bicarbonate. The brown flocculent precipitate was separated and washed, and sublimation of a portion at 100—110° (bath temp.)/$10^{-4}$ mm., followed by crystallisation from aqueous alcohol, yielded the *imino-compound* as leaflets, decomp. *ca.* 230° (Found: C, 49·4; H, 5·8. $C_7H_{10}ON_2S$ requires C, 49·4; H, 5·9%).

5-spirocyclo*Pentyl*-2 : 4-*thiazolidione* (I; $n = 2$).—The bulk of the above crude imino-compound was refluxed with 2N-hydrochloric acid (250 c.c.) for 4—5 hours, the solution was decolorised (charcoal) and on cooling long needles of 5-spirocyclo*pentyl*-2 : 4-*thiazolidione* (11·5 g.) were obtained which, after crystallisation from aqueous alcohol, had m. p. 111—112° (Found: C, 49·1; H, 4·9. $C_7H_9O_2NS$ requires C, 49·1; H, 5·3%). Light absorption: Maximum, 2275A.; $\varepsilon = 4000$. The N-*methyl ether*, prepared by heating the dione (4 g.) with methyl iodide (6 g.) and 2N-sodium hydroxide (12·5 c.c.) in methanol (20 c.c.) in a sealed tube at *ca.* 50° for 42 hours, was purified by sublimation at 40—60° (bath temp.)/ $10^{-4}$ mm. and crystallisation from ligroin (b. p. 60—80°), and formed prisms (2·7 g.), m. p. 53° (Found: C, 51·9; H, 5·9. $C_8H_{11}O_2NS$ requires C, 51·85; H, 6·0%). Light absorption: Maximum, 2280A.; $\varepsilon = 3500$.

5-spirocyclo*Hexyl*-2-*imino*-4-*thiazolidone*.—Attempts to condense ethyl 1-bromo*cyclo*hexane-1-carboxylate with thiourea under a variety of conditions were unsuccessful. When the acid chloride was employed (cf. Doran and Shonle, *loc. cit.*) only the *thioureide* of 1-*bromo*cyclo*hexane*-1-*carboxylic acid* could be isolated. It crystallised from methanol in plates, m. p. 184° (Found: N, 10·55. $C_8H_{13}ON_2BrS$ requires N, 10·55%).

A mixture of thiourea (3 g.; 1·5 mol.), anhydrous sodium acetate (3 g.), 1-bromo*cyclo*hexane-1-carboxylic acid (5·3 g.; Fourneau *et al.*, *Chem. Abstracts*, 1922, **16**, 240) and dioxan (90 c.c.) was refluxed for 7 hours. The hot solution was filtered and the crystalline powder which separated on cooling was recrystallised from aqueous alcohol and hot water giving the *imino-compound* (1·8 g.) as prismatic needles, m. p. 254—256° (slight decomp.) (Found: C, 52·3; H, 6·6; N, 15·55. $C_8H_{12}ON_2S$ requires C, 52·15; H, 6·55; N, 15·2%).

5-spirocyclo*Hexyl*-2 : 4-*thiazolidione* (I; $n = 3$).—A similar experiment to that described above, using bromo-acid (26 g.), in which the crude imino-compound was hydrolysed by refluxing with 2N-hydrochloric acid (250 c.c.) for 2 hours, gave the *thiazolidione* (11·4 g.), crystallising from aqueous alcohol or water as long needles, m. p. 125—126° (Found: C, 51·6, 51·7; H, 6·2, 5·95. $C_8H_{11}O_2NS$ requires C, 51·85; H, 6·0%). Light absorption: Maximum, 2250A.; $\varepsilon = 4500$. The N-*methyl ether*, prepared in 70% yield as described for the *cyclo*pentyl analogue, formed rhombic prisms from ligroin (b. p. 60—80°), with m. p. 55° (Found: C, 54·15; H, 6·6. $C_9H_{13}O_2NS$ requires C, 54·25; H, 6·6%). Light absorption: Maximum, 2280A.; $\varepsilon = 4000$.

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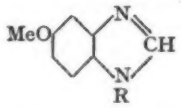
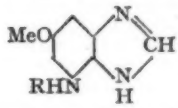
## 25. *New Potential Chemotherapeutic Agents. Part IV. Derivatives of Benziminazole.*

By F. E. King, R. J. S. Beer, and S. G. Waley.

5-*Methoxy*-1-*β-diethylaminoethylbenziminazole* (I; R = $-CH_2{\cdot}CH_2{\cdot}NEt_2$) has been synthesised from 3-amino-4-*β*-diethylaminoethylanisole. A projected synthesis of a benziminazole analogue of pamaquin failed at the final stage owing to unexpected difficulties in the hydrolysis of 7-p-*toluenesulphon*-(*β-diethylaminoethyl*)*amido*-5-*methoxybenziminazole*. Two examples are given of the preparation of 2-chloro-5-hydroxyalkylamino-7-methoxyacridines.

SYNTHESES of methoxylated 1-diethylaminoalkylbenziminazoles have been described by Ochiai and Katada (*J. Pharm. Soc. Japan*, 1940, **60**, 543), Simonov (*J. Gen. Chem. Russia*, 1940, **10**, 1588), and Clemo and Swan (*J.*, 1944, 274), and a synthesis of a 2-β-aminoethylethoxybenziminazole has been described by Chatterjee (*J.*, 1929, 2965). Where any biological data have been reported, these have shown that these compounds are without action on avian malaria; but at the time the following experiments were begun it was not clear whether this was also true for the benziminazoles (I, R = diethylaminoalkyl) unsubstituted at the 2-position. Evidence on this point was obtained by the preparation of *5-methoxy-1-β-diethylaminoethylbenziminazole* (I; R = $-CH_2 \cdot CH_2 \cdot NEt_2$) which proved to be without effect on trophozoite infections due to *P. relictum* in canaries

(I.) 

 (II.)

and *P. gallinaceum* in chicks. This was confirmed when Clemo and Swan (*loc. cit.*) published their work on a number of benziminazoles substituted at the 1-position by the group $-CHMe \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$—among them a homologue of the base (I; R = $-CH_2 \cdot CH_2 \cdot NEt_2$)—all of which were biologically inactive.

The method used for the preparation of (I; R = $-CH_2 \cdot CH_2 \cdot NEt_2$) differs from the procedure of Clemo and Swan and started from 3-nitro-4-*p*-toluenesulphonamidoanisole. As in the synthesis of the corresponding 4-p-*toluenesulphon-(β-diethylaminoethyl)amidoanisole*, the sodium salt of the nitrosulphonamide was alkylated by β-chloroethyldiethylamine in alcoholic solution to give *3-nitro-4-p-toluenesulphon-(β-diethylaminoethyl)-amidoanisole*. From this the toluenesulphonyl group was removed with cold 90% sulphuric acid leaving *3-nitro-4-β-diethylaminoethylaminoanisole*. Hydrogenation over Raney nickel gave the corresponding 3-amino-compound which, without purification, was acidified and converted by heating with formic acid to the benziminazole (I; R = $-CH_2 \cdot CH_2 \cdot NEt_2$), a reddish oil yielding a colourless crystalline hydrochloride.

Experiments were also made to prepare a benziminazole having substituents similar in character and orientation to those of pamaquin, *e.g.* (II; R = $-CH_2 \cdot CH_2 \cdot NEt_2$). These began with the reduction, by hydrogen sulphide in aqueous ammonia, of 3 : 5-dinitro-4-aminoanisole to 5-nitro-3 : 4-diaminoanisole, characterised by a 2 : 3-*diphenylquinoxaline*. By the action on the nitro-diamine of formic and hydrochloric acids, *7-nitro-5-methoxybenziminazole* was obtained and catalytically reduced to the *7-amino-derivative*. For the purpose of alkylation, a p-*toluenesulphonamide* was prepared which, from its solubility in alkali, appears to be the desired product (II; R = *p*-$SO_2 \cdot C_6H_4 \cdot Me$) rather than the 1- or the 3-toluenesulphonamide. Heating with β-chloroethyldiethylamine in alcoholic sodium ethoxide gave a mono-β-diethylaminoethyl derivative (m. p. 179—181°) accompanied, when the reaction was prolonged, by a di-β-diethylaminoethyl compound, probably 7-p-*toluenesulphon-(β-diethylaminoethyl)amido-5-methoxy-1*(or 3)-β-*diethylaminoethylbenziminazole*. From its method of formation the product, m. p. 179—181°, is regarded as the 7-p-*toluenesulphonamide* of (II; R = $-CH_2 \cdot CH_2 \cdot NEt_2$), although the possibility that alkylation has occurred in the 1- or 3-position rather than at the sulphonamido group cannot be entirely excluded. Hydrolysis of the protective group with cold 90% sulphuric acid yielded a basic oil; this was apparently heterogeneous, and the desired benziminazole could not be isolated from it. In view of its unsatisfactory features this work was discontinued.

In the experimental section two examples are given of the preparation of 2-chloro-5-hydroxyalkylamino-7-methoxyacridines. Investigations in this series were suspended when these compounds were shown to be without effect on avian malaria.

## EXPERIMENTAL.

*4-p-Toluenesulphon-(β-diethylaminoethyl)amidoanisole.*—The addition of sodium hydroxide (45 g.) in water (120 c.c.) to a solution of 4-*p*-toluenesulphonamidoanisole (30 g.) in the 3% aqueous alkaline solution (150 c.c.) precipitated the sodium salt (30 g.), which was dried and heated with β-chloroethyldiethylamine hydrochloride (20 g., 1·15 mol.) in a solution of sodium (2·7 g., 1·15 mol.) in absolute alcohol (50 c.c.) under reflux for 32 hours. The filtered liquid was evaporated and, after ether extraction, a light brown oil (22 g.) was obtained and this was converted into 4-p-*toluenesulphon-(β-diethylaminoethyl)amidoanisole hydrochloride*, colourless prisms, m. p. 169°, from alcohol–ether (Found: C, 57·5; H, 7·2; N, 6·5. $C_{20}H_{26}O_3N_2S,HCl$ requires C, 58·1; H, 7·1; N, 6·8%). The *picrolonate* separated in pale yellow aggregates, m. p. 131—132° (Found: C, 56·1; H, 5·6. $C_{30}H_{36}O_8N_6S$ requires C, 56·2; H, 5·6%).

*3-Nitro-4-p-toluenesulphon-(β-diethylaminoethyl)amidoanisole.*—The sodium derivative of 3-nitro-4-*p*-toluenesulphonamidoanisole was prepared by adding a solution of sodium (3·45 g., 1 mol.) in alcohol (100 c.c.) to the amide (48 g., 1 mol.) also dissolved in hot alcohol (300 c.c.). β-Chloroethyldiethylamine (27·5 g., 1·25 mol.) was then introduced and the solution refluxed on a steam-bath for 48 hours. Alcohol was removed from the filtered solution, and the syrupy residue shaken with 2N-sodium hydroxide and ether. The product obtained by evaporating the ether layer, when triturated with light petroleum, gave yellow microcrystalline plates (65 g., 91%), m. p. 44·5—46·5°, and was identified as 3-nitro-4-*p*-toluenesulphon-(β-diethylaminoethyl)amidoanisole by means of the *picrate*, which crystallised from ethanol in yellow needles, m. p. 154° (Found: C, 48·0; H, 4·7. $C_{26}H_{30}O_{13}N_6S$ requires C, 48·0; H, 4·6%).

*3-Nitro-4-β-diethylaminoethylaminoanisole.*—The above sulphonamide (10 g.) was dissolved in sulphuric acid (40 c.c. of 90%) at 0° and left overnight. The product obtained by pouring on to ice (100 g.) and basifying with ammonia was extracted with ether. Evaporation of the dried solution gave 3-nitro-4-β-diethylaminoethylanisole which formed blood-red needles, m. p. 42° (5·6 g., 88%), characterised by the *picrate*, crystallising from acetone in long, thin, orange-red prisms, m. p. 181° (decomp.) (Found: C, 45·5; H, 4·6. $C_{19}H_{24}O_{10}N_6$ requires C, 46·0; H, 4·8%).

*5-Methoxy-1-β-diethylaminoethylbenziminazole.*—The alkylated nitroanisidine (1·87 g.) dissolved in alcohol was hydrogenated over Raney nickel at normal temperature and pressure; a colourless liquid was obtained from which the crude diamine hydrochloride was isolated by evaporation of the filtered and acidified solution. The free base was refluxed with formic acid (2 g., 6 mol.) in an oil-bath at 120° for 6 hours. Aqueous sodium hydroxide (10 c.c., 40%) liberated the *benziminazole* which distilled at 145—165° (air-bath temp.)/0·1 mm. as a red oil (Found: C, 67·6; H, 8·6. $C_{14}H_{21}ON_3$

requires C, 68·0; H, 8·5%). The hydrochloride (0·65 g., 30%) precipitated from a solution of the base in dry ether, after 3 crystallisations from ethanol–ethyl acetate consisted of colourless needles, m. p. 203° (evacuated capillary).

5-*Nitro*-3 : 4-*diaminoanisole*.—A suspension of powdered 3 : 5-dinitro-4-aminoanisole (10 g.) in ethanol (200 c.c.) and aqueous ammonia (4 c.c., *d* 0·88) was repeatedly saturated with hydrogen sulphide and heated to boiling until the red nitro-compound was no longer visible. Finally the boiling liquid was filtered from sulphur and the product, which separated on standing, was washed with carbon disulphide leaving the 5-nitro-3 : 4-diaminoanisole as dark red needles (6·6 g., 63%), which, after crystallisation from ethanol, had m. p. 181—182°. When heated in ethanol with benzil and sodium acetate, the sparingly soluble 8-*nitro*-6-*methoxy*-2 : 3-*diphenylquinoxaline* separated as green–yellow needles, m. p. 239—241°, after recrystallisation from ethanol (Found: C, 70·2; H, 4·3. $C_{21}H_{15}O_3N_3$ requires C, 70·6; H, 4·2%).

7-*Nitro*-5-*methoxybenziminazole*.—5-Nitro-3 : 4-diaminoanisole (2 g.), formic acid (1 c.c.) and 4N-hydrochloric acid (20 c.c.) were heated under reflux, and in 30 minutes more formic acid (1 c.c.) was added. After 1 hour's refluxing the cooled solution was neutralised with ammonia, and the precipitated *benziminazole* crystallised from ethanol, giving yellow rectangular plates (1 g., *ca.* 50%) subliming > 250° (Found: C, 49·7; H, 3·6. $C_8H_7O_3N_3$ requires C, 49·7; H, 3·6%). Owing to the insolubility of the base larger quantities were more easily purified by recrystallisation of the hydrochloride, which separated from dilute hydrochloric acid in a felted mass of yellow needles, decomp. 100°. The salt lost hydrogen chloride on drying or heating and was hydrolysed by hot water.

7-*Amino*-5-*methoxybenziminazole*.—The nitro-iminazole (0·2 g.) suspended in methanol was hydrogenated at 50°/30 atms. over Raney nickel. Difficulties, sometimes encountered in the reductions, were overcome by first refluxing a suspension of the nitro compound in methanol with Raney nickel for 1 hour. After reduction, evaporation of the filtered solution left a brown oil which did not crystallise but gave the amino-iminazole *monopicrate* crystallising from ethanol as an orange powder, m. p. *ca.* 240° (decomp.) (Found: C, 43·3; H, 2·9. $C_{14}H_{12}O_8N_6$ requires C, 42·9; H, 3·1%).

The product obtained by heating the amino-iminazole with *p*-toluenesulphonyl chloride and pyridine at 100° for 1 hour, treated with water and crystallised from ethanol, gave 7-p-*toluenesulphonamido*-5-*methoxybenziminazole* as a grey crystalline powder, m. p. 244—246° (decomp.). When pure, it separated in tiny colourless needles, m. p. 248° (decomp.) (Found: C, 56·7; H, 5·0; N, 13·4; S, 9·9. $C_{15}H_{15}O_3N_3S$ requires C, 56·8; H, 4·7; N, 13·2; S, 10·1%).

7-p-*Toluenesulphon*-(β-*diethylaminoethyl*)*amido*-5-*methoxybenziminazole*.—The sulphonamidobenziminazole (0·92 g.) and β-chloroethyldiethylamine hydrochloride (0·5 g.) were added to a solution of sodium (0·13 g., 2 mol.) in ethanol, and the mixture refluxed for 22 hours. By treatment with water and ether extraction, a pale brown oil (0·8 g.) was isolated which solidified on trituration with ligroin, in which the product, m. p. *ca.* 170°, was sparingly soluble. By recrystallisation from ethanol–ligroin the *sulphon*-β-*diethylaminoethyl*-*amide* gave colourless needles, m. p. 179—181° (decomp.) (Found: C, 60·8; H, 6·9; S, 7·7. $C_{21}H_{28}O_3N_4S$ requires C, 60·6; H, 6·7; S, 7·7%). A repetition of this experiment with the sulphonamide (2·85 g.) and refluxing for 48 hours gave a more resinous product from which extractions with warm ligroin gave colourless plates (0·2 g.), m. p. 120°, of the dialkylated sulphonamide, readily soluble in dilute mineral acid and insoluble in aqueous alkali (Found: C, 63·2; H, 7·7; N, 14·0. $C_{27}H_{41}O_3N_5S$ requires C, 62·9; H, 8·0; N, 13·6%). Crystallisation of the insoluble (in ligroin) fraction gave a pale brown solid (0·3 g.), m. p. 170—177° which, after further crystallisation from ethanol–ligroin, had m. p. 179—181°, alone or mixed with the mono-alkylated sulphonamide.

7-*p*-Toluenesulphon-(β-diethylaminoethyl)amido-5-methoxybenziminazole (0·13 g.) was dissolved in 90% sulphuric acid (1 c.c.) and set aside for some hours. The dark liquid was poured on ice and the solution basified. By ether extraction a brown oil was isolated and this with alcoholic picric acid gave a sparingly soluble orange solid. Crystallisation from acetone gave an inseparable mixture of yellow rhombs and red prisms, the proportions of which were not affected by varying the amount of picric acid used.

2-*Chloro*-5-*amino*-7-*methoxyacridine Hydrochloride*.—This aminoacridine was prepared by the general method of Albert and Ritchie (*Org. Synth.*, 1942, **22**, 5), a solution of 2 : 5-dichloro-7-methoxyacridine (2·8 g.) in phenol (15 g). at 70° being treated with ammonium carbonate (0·9 g.) and heated at 120—130° for 10 minutes. The cooled mixture was treated with ethanol (5 c.c.) and concentrated hydrochloric acid (2 c.c.) and then diluted with ether (50 c.c.), the *aminoacridine hydrochloride* separating as slender yellow needles (3·2 g., 95% yield), m. p. 260°. It was sparingly soluble and was purified by continuous extraction with methanol (Found: C, 56·8; H, 4·3. $C_{14}H_{11}ON_2Cl,HCl$ requires C, 56·95; H, 4·1%).

2-*Chloro*-5-β-*hydroxyethylamino*-7-*methoxyacridine*.—Ethanolamine (2·4 g.), 2 : 5-dichloro-7-methoxyacridine (5·6 g.) and phenol (15 g.) were heated together on the steam-bath for 2 hours. The reaction mixture was diluted with ethanol (20 c.c.), concentrated hydrochloric acid (2 c.c.) and ether (20 c.c.), and the precipitated solid purified by extraction with methanol. The *acridine hydrochloride* formed golden prisms, m. p. 235—237° (decomp.) (Found: C, 56·9; H, 4·8; N, 7·8. $C_{16}H_{15}O_2N_2Cl,HCl$ requires C, 56·6; H, 4·7; N, 8·3%). Treatment of the hydrochloride dissolved in phenol with aqueous sodium hydroxide gave the free base which crystallised from aqueous ethanol in orange needles, m. p. 189—192° (Mietzsch and Mauss, *Chem. Abstr.*, 1932, **26**, 4684, give m. p. 191—192°).

γ-*Hydroxy*-n-*propylamine*.—2-Cyanoethanol (*Org. Synth.*, 1923, **3**, 57) (10 g.) in alcoholic ammonia (100 c.c.) was hydrogenated at high pressure over Raney nickel, the temperature rising to 90° during 2 hours. The filtered solution was distilled to give the propanolamine (7 g., 67%), b. p. 185—189° (Putochin, *Ber.*, 1926, **59**, 605, gives b. p. 185—186°) (Found: C, 48·0; H, 12·0. Calc. for $C_3H_9ON$: C, 48·0; H, 12·0%).

2-*Chloro*-5-γ-*hydroxy*-n-*propylamino*-7-*methoxyacridine Hydrochloride*.—The propanolamine (3 g.), 2 : 5-dichloro-7-methoxyacridine (5·6 g.) and phenol (20 g.) were heated at 120—130° for 2 hours, and the *hydrochloride* (9·5 g.) isolated as in the case of the lower homologue. After purification by repeated digestion with acetone it had m. p. 241—243° (decomp.) (Found: C, 57·7; H, 5·4. $C_{17}H_{17}O_2N_2Cl,HCl$ requires C, 57·8; H, 5·1%).

The two hydroxyalkylaminoacridines proved inactive when tested against *P. relictum* in canaries and *P. gallinaceum* in chicks. For the biological tests we thank Miss A. Bishop, Molteno Institute, Cambridge, and Miss I. M. Tonkin, National Institute of Medical Research, London.

Dyson Perrins Laboratory, Oxford. [*Received, November 8th*, 1945.]

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## 26. 6-*Aminoacetoveratrone and* 5 : 6-*Dimethoxy*-3-*methylanthranil.*

By J. C. E. Simpson.

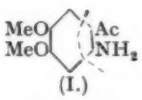
According to conditions of reduction, 6-nitroacetoveratrone is converted into either of two substances, m. p. 133° and 108°, or into a mixture of both these products. Each of these compounds has been designated as 6-aminoacetoveratrone (I), the former by Lawson, Perkin, and Robinson (*J.*, 1924, **125**, 626), and the latter by

Mannich and Berger (*Arch. Pharm.*, 1939, **277**, 117); the German authors regard the substance, m. p. 133°, as the anthranil (III).

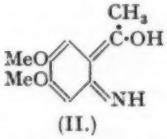
Experiments are described which indicate that the conclusions of Mannich and Berger are correct.*

DURING a review of existing *o*-aminoacetophenones (*J.*, 1945, 646), a study was made of the preparation and properties of the substance, m. p. **133°**, prepared by Lawson, Perkin, and Robinson (*loc. cit.*) by reduction of 6-nitroacetoveratrone and designated 6-aminoacetoveratrone (I) by these authors.

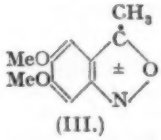
The best method for the preparation of acetoveratrone appears to be that of Koepfli and Perkin (*J.*, 1928, 2989); substitution of acetic anhydride for acetyl chloride, which Noller and Adams (*J. Amer. Chem. Soc.*, 1924, **46**, 1889) have shown usually effects a marked improvement in the preparation of substituted acetophenones, gave inferior yields in this case. Nitration of the ketone to 6-nitroacetoveratrone was, surprisingly, always unsatisfactory under the conditions of Lawson, Perkin, and Robinson (*loc. cit.*) [substantially the same conditions are also described by Mannich and Berger (*loc. cit.*)], but consistently high yields were obtained by slightly modifying these conditions. For the reduction of the nitro-ketone, these authors used a stoicheiometric deficiency of stannous chloride, but made no mention of unchanged nitro-compound, which, in a repetition of their work, was always found to be present with the substance, m. p. **133°**. When stannous chloride was employed in excess, no unchanged nitro-compound was isolated, the products of the reaction being the compound, m. p. **133°**, and a second substance, m. p. **106—108°**, analysis of which indicated an empirical formula $C_{10}H_{13}O_3N$. This substance gave an acetyl derivative, m. p. **128°**, from which it could be regenerated by acid hydrolysis; it was formed as the sole isolable product when 6-nitroacetoveratrone was reduced by West's method (*J.*, 1925, **127**, 494) or with iron and acetic acid.



(I.)



(II.)



(III.)

6-Nitroacetoveratrone forms an anisylidene derivative (Lawson, Perkin, and Robinson, *loc. cit.*), and a *furfurylidene* derivative was similarly produced in presence of alcoholic potassium hydroxide; piperidine failed to effect condensation with anisaldehyde. The reduction product, m. p. **133°**, on the other hand, failed to give either a chalkone or a Schiff base with anisaldehyde under alkaline conditions (piperidine or potassium hydroxide), and it resisted acetylation under normal conditions. The assumption that the portion of the molecule indicated by the broken line in (I) might function as a "vinylogue" of a neutralised system [Robinson, "Outline of an Electrochemical (Electronic) Theory of Organic Reactions," 1932, p. 27], $\overset{|}{C}(NH_2):\overset{|}{C}\cdot\overset{|}{C}O$, is not an explanation of this lack of reactivity, because *o*-aminoacetophenone has long been known to acetylate normally (Baeyer and Bloem, *Ber.*, 1882, **15**, 2147)—the reaction is in fact appreciably exothermic—and Mannich and Dannehl (*Ber.*, 1938, **71**, 1899) have prepared 2-aminochalkone from *o*-aminoacetophenone and benzaldehyde. [Incidentally, these authors do not comment on the fact that their aminochalkone, m. p. 71°, is different from the substance, m. p. 147°, to which the same constitution was previously ascribed by Engler and Dorant (*Ber.*, 1895, **28**, 2497); the discrepancy is possibly explained by geometrical isomerism, as the substances were prepared by different methods.] A feasible structure for the substance, m. p. **133°**, appeared to be (II), arising from (I) by tautomeric change (theoretical considerations suggest that this could readily occur), and this structure received superficial support from the observation that 80% of the substance, m. p. **133°**, was recovered from reaction with excess of ethylmagnesium bromide under "inverse" conditions at room temperature [a resinous product was formed when the substance in ether was added to a large excess of alkylmagnesium halide under reflux; β-(2-amino-4 : 5-dimethoxybenzoyl)-propionic acid and its ethyl ester (Schofield and Simpson, *J.*, 1945, 520) also gave non-crystalline products when added to a large excess of methylmagnesium iodide]. The compound also reacted with maleic anhydride in boiling xylene, but not in boiling benzene; the product of this reaction was a dark resin, which gave an amorphous acid on hydrolysis.

An alternative suggestion as to the structure of the compound, m. p. **133°**, has been made by Mannich and Berger (*loc. cit.*). They regard this substance as the anthranil (III),† and assign the constitution (I) to a compound, m. p. **107°**, which they obtained as the sole product of the catalytic reduction of 6-nitroacetoveratrone. As Mannich and Berger's compound, m. p. **107°**, gave analytical figures in agreement with the formula $C_{10}H_{13}O_3N$, and yielded an acetyl derivative, m. p. **127·5°**, there can be no doubt that the substance is identical with the compound, m. p. **106—108°**, prepared during the present work by reduction of 6-nitroacetoveratrone, but under different conditions.

Mannich and Berger's assignment of structures (III) and (I) to the compounds, m. p. **133°** and **107°**, is based, in addition to analytical data, on statements that the former may be reduced to the latter, and that the corresponding indigo derivative was obtained from the acetamido-compound, m. p. **127·5°**, *via* the ω-bromo-

* Sir Robert Robinson has kindly informed the author that results of work in his laboratory subsequent to the original publication are in agreement with the conclusions reached in this paper. The amount of stannous chloride used was much greater than stated and the product, as shown *inter alia* by the reactions cited, was largely the amino-ketone. Crystallisation afforded a relatively small yield of the substance, m. p. 133°.

† The modified formula (III) is suggested as a convenient symbol for giving expression to the considerations outlined by Baker (*J.*, 1945, 267) respecting the structure of such substances.

derivative. However, these authors have not recorded experimental support for these statements, and independent evidence to settle the point was therefore sought.

That the substance, m. p. 107°, is correctly formulated as (I) was demonstrated by nitration of the *N*-acetyl derivative, m. p. 128°; this led to elimination of the *C*-acetyl group with formation of 4-nitro-5-acetamidoveratrole (for examples of the elimination of carboxyl or *C*-acetyl groups during nitration, see Harding, *J.*, 1911, 1585; 1914, 2790; Simonsen *et al.*, *J.*, 1917, 71; 1918, 22; Lawson, Perkin, and Robinson, *loc. cit.*, p. 653). It was also found that the substance, m. p. 133°, is converted, like 6-nitroacetoveratrone, into 6-aminoacetoveratrone by treatment with iron and acetic acid, and that it yielded a mixture of the aminoketone and the *oxime* of the latter on treatment with hydroxylamine; it is therefore an intermediate stage in the reduction of the nitro- to the amino-ketone, and is thus correctly formulated, in accord with the statement of Mannich and Berger, as the anthranil (III).

## Experimental.

(M. p.'s are uncorrected.)

6-*Nitroacetoveratrone.*—Application of the general method of Noller and Adams to the preparation of acetoveratrone was unsatisfactory; from veratrole (70 g.) and acetic anhydride (55 g.) the former (28 g.) was recovered, and the ketone (26·5 g.) isolated represented a yield of 48% based on reacted veratrole. The use of nitrobenzene as solvent gave variable results, the best being a 51% yield with no recovery of veratrole. Acetoveratrone invariably had b. p. 168—169°/14 mm., in agreement with the value found by Koepfli and Perkin (b. p. 160—162°/10 mm., *loc. cit.*); the figures given in Heilbron's "Dictionary of Organic Compounds" (1st. Edition) and by Pictet and Gams (*Ber.*, 1909, **42**, 2947) are evidently erroneous (205—207°/10—15 mm. and 206°/12 mm. respectively). In the literature method for the nitration of acetoveratrone, nitric acid (*d* 1·42) alone was used as the nitrating agent; the best result obtained in several repetitions of the method was 4·6 g. of nitro-ketone from 10 g. of acetoveratrone. The following conditions gave an 86% yield of recrystallised product. Powdered acetoveratrone (13·5 g.) was added in portions during 10—12 minutes to a mechanically-stirred mixture of nitric acid (47 c.c., *d* 1·42) and concentrated sulphuric acid (20 c.c.), the reaction temperature being kept between −5° and −3°. The nitro-ketone usually (but not always) began to crystallise after the last of the ketone had been added, and after ½ hour the mass was poured into water and recrystallised from alcohol (14·5 g., m. p. 133·5—135°).

The furfurylidene derivative was prepared by warming a mixture of the ketone (5 g.), furfural (3·5 c.c.), and alcohol (50 c.c.) until most of the solid had dissolved. Addition of aqueous potassium hydroxide (1 c.c., 30%) produced much evolution of heat, and a crystalline mass separated. After washing with cold alcohol, almost pure *furfurylidene derivative* (5·85 g., 87%) was obtained, very sparingly soluble in alcohol, and separating from aqueous acetic acid in long pale yellow needles, m. p. 150—151° (Found: C, 59·4; H, 4·7; N, 5·1. $C_{15}H_{13}O_6N$ requires C, 59·4; H, 4·3; N, 4·6%).

The anisylidene derivative (yield, 79%) formed small lemon-yellow needles, m. p. 168—169°, from aqueous acetic acid (Lawson, Perkin, and Robinson, *loc. cit.*, give m. p. 170°) (Found: C, 62·95; H, 5·05. Calc. for $C_{18}H_{17}O_6N$: C, 63·0; H, 5·0%). No reaction between the ketone and anisaldehyde occurred in hot alcoholic solution when piperidine was used in place of potassium hydroxide.

*Reduction Experiments with* 6-*Nitroacetoveratrone.*—(a) Reduction by the stannous chloride method of Lawson, Perkin, and Robinson (*loc. cit.*) was incomplete; 5 g. of ketone gave unchanged material (1·65 g.) and the anthranil (1·85 g.). Replacement of half of the hydrochloric acid by the same volume of glacial acetic acid had little effect on the yield (1 g. of nitro-compound recovered and 1·8 g. of anthranil). (b) Using excess stannous chloride, 6-aminoacetoveratrone was formed. A finely-divided suspension of the nitro-ketone (5 g.) in acetic acid (25 c.c.) was treated with a solution of stannous chloride (22 g.) in concentrated hydrochloric acid (28 c.c.). After an hour, fine colourless needles separated on scratching; this material was collected after a further 2 hours and yielded anthranil [1·85 g., m. p. 131—132·5° alone and mixed with authentic material prepared by method (a)] after decomposition with alkali and recrystallisation from methanol. A sample prepared for analysis from aqueous alcohol formed small, almost colourless prisms, m. p. 133—134° [Found: C, 61·8; H, 5·5. Calc. for $C_{10}H_{11}O_3N$ (anthranil): C, 62·15; H, 5·75. Calc. for $C_{10}H_{13}O_3N$ (amino-ketone): C, 61·5; H, 6·7%]. The filtrate from the stannichloride was treated with excess potassium hydroxide and extracted with ether until the extracts were colourless. The ethereal solution was washed twice with a little water, dried and evaporated, yielding crude crystalline material (1 g.); this was very soluble in alcohol, easily so in hot water, and considerably less so in ether. After crystallisation from ether containing a little alcohol and finally from ether alone, 6-aminoacetoveratrone separated in very pale yellow, slender, dull needles, m. p. 106—108° (depressed when mixed with either the nitro-ketone or the anthranil) (Found: C, 61·1; H, 6·7; N, 7·6. Calc. for $C_{10}H_{13}O_3N$: C, 61·5; H, 6·7; N, 7·2%). When heated with acetic anhydride (10 c.c.) at 95° for 1½ hours, the amine (4 g.) gave the acetyl derivative (3·8 g.); this substance was very soluble in alcohol and hot water, and formed fine, colourless, woolly needles, m. p. 127—128°, from benzene–ligroin (b. p. 60—80°) (Found: C, 61·45; H, 6·5; N, 6·3. Calc. for $C_{12}H_{15}O_4N$: C, 60·75; H, 6·4; N, 5·9%). It was reconverted into the amine by heating for 1 hour at 100° with a mixture of concentrated (10 parts) and 2N-hydrochloric acid (20 parts); after addition of ammonia and crystallisation from aqueous methanol, the base had m. p. and mixed m. p. 106—108°. (c) A boiling solution of 6-nitroacetoveratrone (2·25 g.) in methylated spirit (15 c.c.) and concentrated hydrochloric acid (0·5 c.c.) was treated with iron filings (2 g., added in 4 portions at 5-minute intervals). After being refluxed for 2½ hours, the suspension was made alkaline with aqueous sodium hydroxide and extracted 5 times with ether. The washed and dried extracts, on evaporation, gave a residue which furnished the amine (1·5 g.) from ether containing a little benzene; m. p. and mixed m. p. 106—107° after recrystallisation (Found: C, 60·8; H, 6·9; N, 7·4%). (d) The nitro-ketone (5 g.) in acetic acid (40 c.c.) was treated on the steam-bath with iron filings (7·5 g.), added in portions during 1 hour with frequent shaking; additions of 10 c.c. portions of water were made at the start of the reaction and after ¾ hour. After a total of 1½ hours, the mixture was diluted with water and the product isolated by ether-extraction, yielding once crystallised material (3·2 g.), m. p. 103—105° (identified by mixed m. p.).

*Oxime of* 6-*Aminoacetoveratrone.*—Prepared from the ketone (1 part), hydroxylamine hydrochloride (1·5 parts), and fused sodium acetate (2 parts) in boiling aqueous alcoholic solution, the *oxime* was obtained in fine colourless needles, m. p. 154·5—156° after crystallisation from hot water (Found: C, 56·95; H, 6·4; N, 13·55. $C_{10}H_{14}O_3N_2$ requires C, 57·1; H, 6·7; N, 13·3%).

*Experiments with* 5 : 6-*Dimethoxy*-3-*methylanthranil.*—(a) From attempts to condense the substance with anisaldehyde in presence of either piperidine or potassium hydroxide in alcohol, unchanged material (the only isolable product) was recovered to the extent of 45—60%. (b) A solution of the substance (0·6 g.), hydroxylamine hydrochloride (0·9 g.), and fused sodium acetate (1·2 g.) in 50% aqueous alcohol (12 c.c.) was refluxed for 1½ hours; solvent was then removed in an evacuated desiccator until crystallisation occurred. The crude oxime of 6-aminoacetoveratrone (0·35 g.) was crystallised several times from hot water, from which it separated in soft colourless needles, m. p. 154—155·5°, not depressed on mixing with the specimen described above. The original filtrate on further concentration gave 0·3 g. of easily-soluble material. From this, some of the foregoing oxime was removed by crystallisation from a little water;

the material in the filtrate was then isolated and crystallised from ether–ligroin (b. p. 40—60°), giving pale yellow needles, m. p. 105—107° alone and mixed with 6-aminoacetoveratrone (Found : C, 61·5; H, 6·4; N, 7·5%). (c) The product obtained by reduction at 85° of the anthranil (0·5 g.) in acetic acid (5 c.c.) with iron powder (0·7 g.) [water (6 c.c.) was added in portions during the reaction] was isolated by dilution with water and extraction with chloroform. The residue from the washed, dried, and evaporated extract was taken up in ether and yielded the amino-ketone (0·25 g.), m. p. and mixed m. p. 106—107°. (d) The anthranil (300 mg.) and maleic anhydride (300 mg.) were heated with xylene (3 c.c.) (cf. Schönberg and Mostafa, *J.*, 1943, 654); a dark solution was formed, followed by gradual deposition of a dark resinous solid. After 3 hours' refluxing and leaving the mixture for 48 hours, the xylene was decanted from the resin and crystalline matter which had separated. The whole residue was heated at 95° for 1 hour with 2N-aqueous sodium hydroxide, and then extracted with ether. The extract gave unchanged anthranil (50 mg.) and the alkaline solution, on acidification, yielded a dark amorphous solid (130 mg.), m. p. 240—260° (decomp.), easily soluble in glacial acetic acid, and separating in amorphous form on gradual dilution with water.

*Nitration of 6-Acetamidoacetoveratrone.*—The acetamido-ketone (1·5 g.) was added during 12 minutes to 10 c.c. of a mixture of nitric acid (10 c.c., *d* 1·42), acetic acid (4 c.c.), and water (2 c.c.) at a temperature not exceeding −10°; crystallisation of the product set in after about half the material had been added. After 18 minutes from the start of the experiment, the paste was poured on to ice, and the solid recrystallised from alcohol, yielding soft golden needles (1·25 g.) of 4-nitro-5-acetamidoveratrole, m. p. 196—197° [lit. m. p.'s, 196° (Simonsen and Rau, *J.*, 1918, 22); 199° (Jones and Robinson, *J.*, 1917, 903)]. Hydrolysis with a mixture of equal volumes of alcohol, water, and concentrated hydrochloric acid (boiled for ½ hour) gave 4-nitro-5-aminoveratrole, which separated from alcohol in orange-red needles, m. p. 173—174° (Found : N, 14·6. Calc. for $C_8H_{10}O_4N_2$: N, 14·1%). Simonsen and Rau, *loc. cit.*, give m. p. 171°, and Jones and Robinson, *loc. cit.*, record m. p. 175°.

Grateful acknowledgment is made of a grant from the Research Fund of the Durham Colleges, and of various facilities kindly afforded by Imperial Chemical Industries, Limited (Dyestuffs Division).

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM. [*Received, October 30th,* 1945.]

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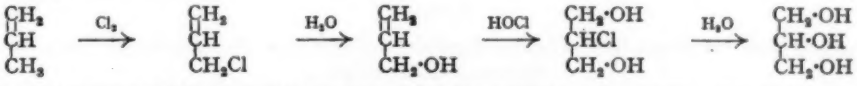
## 27. *Syntheses of* (1) *Glycerol and Propylene Glycol from Propylene, and* (2) *Ethylene Glycol from Ethylene.*

By D. M. NEWITT and P. S. MENE.

In the early stages of the slow combustion of an olefin at high pressures there is formed a mixture of the corresponding oxide and the isomeric aldehyde and alcohol. Under appropriate conditions of temperature and pressure the oxide is hydrolysed to glycol and the alcohol is further oxidised and hydrolysed to a polyhydric alcohol. For instance, propylene gives propylene glycol and glycerol, and ethylene gives ethylene glycol. The effect of temperature, pressure, and other factors on the course of the combustion is described.

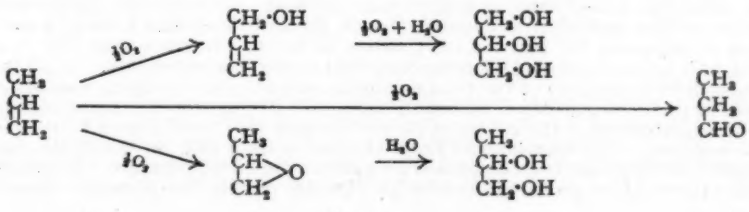
OLEFIN hydrocarbons, available in large quantities from petroleum-cracking, are by virtue of their structure suitable starting materials for the syntheses of certain unsaturated and polyhydric alcohols and of glycols; as an example, glycerol may be prepared from propylene by first chlorinating it at a relatively high temperature (500°), hydrolysing the allyl chloride, and chlorhydrinating the resultant alcohol in aqueous solution (Williams, *Chem. and Met. Eng.*, Dec. 1940) :



In this series of changes allyl alcohol is produced by the addition of oxygen, and glycerol by the addition of water and oxygen, to the parent hydrocarbon, chlorine being the agent used for introducing hydroxyl groups into the molecule. We have found that a similar result may be brought about by simple homogeneous or heterogeneous oxidation and hydrolysis at elevated pressures with or without the presence of added water.

Under appropriate conditions of temperature, pressure, and oxygen concentrations olefins give initially, or in the early stages of their slow combustion, the corresponding oxides together with isomeric aldehydes and alcohols—the relative amounts of the three isomers surviving being determined, partly, by the experimental conditions. The homogeneous oxidation cannot, however, be entirely arrested at this point, and complex changes subsequently take place resulting in the formation of polyhydric alcohols, glycols, lower aldehydes, acids, the two oxides of carbon, and steam. If the oxygen present is insufficient for complete combustion, or if the reaction is curtailed, varying quantities of all the stable intermediate and final products of the oxidation survive and can be isolated and identified.

A detailed analysis of the condensable products from such an oxidation of propylene has revealed the presence of appreciable amounts of propaldehyde, propylene glycol, and glycol, the last two apparently having been formed by secondary reactions from propylene oxide and allyl alcohol, respectively, according to the following scheme :



Ethylene behaves similarly, the initial stable products of its oxidation being ethylene oxide and acetaldehyde; vinyl alcohol may also, possibly, be formed, although attempts to isolate it have hitherto proved unsuccessful (Bone *et al.*, *Proc. Roy. Soc.*, 1933, *A*, **143**, 16). At high pressures and in the presence of steam the oxide is almost completely converted into ethylene glycol.

Although the present communication does not deal with the catalytic combustion of the olefins, it will be recalled that highly selective catalysts are known which will arrest the oxidation of ethylene and propylene at an early stage, giving high yields of the corresponding oxide or glycol.

## Experimental.

To study experimentally slow-combustion processes over a wide pressure range it is necessary to resort to metal reaction vessels and auxiliary equipment, and the results may, therefore, be modified to some extent by surface reactions preceding or taking place concurrently with gas-phase reactions. In the present instance, however, it has been shown that such surface effects are small, and lining the reaction chamber with copper or silica, or partly filling it with steel shavings, does not appear to alter appreciably the general character of the combustion.

The apparatus employed is similar to that previously described (J., 1937, 1666). The hydrocarbon and air or oxygen are stored separately under pressure in steel cylinders; they are introduced directly into the reaction vessel through a fine-adjustment inlet valve, the quantities being determined by measuring their respective partial pressures. The cylindrical reaction vessel is fabricated of an austenitic stainless steel and has a capacity of *ca.* 500 c.c.; it is completely enclosed in an electric furnace so wired as to compensate for the large end losses. Temperatures are measured by a platinum–rhodium thermocouple placed in a thin-walled, steel pocket traversing axially the reaction chamber.

In carrying out a typical experiment, the reaction vessel is first heated to the desired temperature, evacuated, and the requisite amounts of hydrocarbon and oxygen or air admitted separately through the inlet valve. The course of the reaction may then be followed by analysing samples withdrawn at suitable intervals or, in some instances, by observing the temperature changes in the vessel. At the conclusion of reaction or at any pre-selected time, the contents of the vessel are released through the outlet valve, the condensable and the water-soluble products being separated and collected in a train of cooling coils and scrubbers, and the gaseous products sampled and metered. The methods employed in the analysis of the products are described later.

The propylene used was purchased in cylinders from the Ohio Co. of America and, by analysis, was found to contain 99·5% of the hydrocarbon. A cylinder of specially purified ethylene was purchased from the British Oxygen Co. and found to contain 99·7% of the hydrocarbon. Both gases were used without further purification.

*The Slow Oxidation of Propylene.*—When a propylene–oxygen mixture containing excess of the hydrocarbon is raised to such a temperature that reaction ultimately will occur, there is a time "lag" during which no detectable change takes place, followed by a period of uniform slow combustion during which the greater part of the oxygen is consumed. As the temperature is progressively raised, the "lag" shortens and the subsequent reactions speed up until eventually the medium becomes self-heating and ignition may occur. In all the experiments described below, however, the conditions (unless otherwise stated) are such as to ensure substantial constancy of temperature. In general, upwards of 90% of the oxygen is used up, about 60% appearing in the products as condensable vapours (including water) and the remainder as the two oxides of carbon. In the tabulated results the yields are expressed as percentages of the total oxygen in the initial mixture appearing as oxides of carbon, and percentages of the total oxygen in the condensable products appearing as total aldehydes, total acids, propylene glycol, and glycerol.

In Table I the data for various propylene–oxygen and air media reacting at temperatures between 215° and 260° are summarised. In all cases the partial pressure of the hydrocarbon in the initial mixture is 8 atm. and those of the oxygen and nitrogen are as stated.

### Table I.

*Products from the Reaction of Various Propylene–Oxygen (or Air) Media at Temperatures between 215° and 260°.*

(Partial pressure of propylene = 8 atm.)

| Initial mixture, $C_3H_6 : O_2 : N_2$. | Total press., atm. | Reaction temp. | % of total oxygen appearing in products as: $CO_2$. | % of total oxygen appearing in products as: CO. | % of oxygen in condensable product appearing as: Total aldehydes. | Total acids. | Propylene oxide and glycol. | Glycerol. | By diff. (mainly $H_2O$). |
|---|---|---|---|---|---|---|---|---|---|
| 4 : 3 : 0 | 14 | 215° | 30·2 | 8·1 | 7·4 | 20·5 | 1·1 | 2·2 | 68·8 |
| 4 : 2 : 0 | 12 | 215 | 29·1 | 6·9 | 11·0 | 13·2 | 2·2 | 4·9 | 68·7 |
| 4 : 1 : 0 | 10 | 215 | 36·5 | 5·9 | 16·0 | 12·3 | 4·6 | 7·4 | 59·7 |
| 4 : 1 : 0 | 10 | 250 | 33·9 | 7·5 | 16·7 | 5·9 | 3·6 | 6·5 | 67·3 |
| 4 : 1 : 3·8 | 17·6 | 230 | 30·2 | 8·8 | 16·4 | 9·4 | 11·8 | 4·1 | 58·3 |
| | | 250 | 26·5 | 13·3 | 16·8 | 6·2 | 8·8 | 4·3 | 63·9 |
| | | 260 | 20·8 | 22·3 | 20·0 | 2·3 | 5·5 | 4·2 | 68·0 |

Considering first the propylene–oxygen experiments, it will be observed that the yields of those products which are formed in the early stages of the combustion, *viz.*, the aldehydes, glycol, and glycerol, increase with the concentration of the hydrocarbon, whilst the acids formed at a later stage diminish. For instance, by increasing the propylene from 57% to 80% the yield of total aldehydes is doubled, that of glycerol more than trebled, and that of glycol increased four-fold. The effect of increasing the reaction temperature of the 4 : 1 mixture from 215° to 250° is to diminish the yields of acids, glycol, and glycerol and slightly to increase that of the total aldehydes. In all the experiments included in this series, from one-third to one-half of the total aldehyde content of the products consists of formaldehyde, whilst some 80% of the gaseous products consists of carbon dioxide. No free hydrogen is found amongst the gases.

The influence of temperature upon the course of the combustion may best be seen by reference to the data for the 4 : 4·8 propylene–air mixtures. The temperature range covered is from 230°, at which the reaction is comparatively slow, to 260°, at which it is rapid and is accompanied by a slight rise of temperature. On progressively increasing the temperature from 230° the yields of glycol and total acids diminish rapidly, the glycerol remains fairly constant, whilst

the total aldehydes increase; the ratio $CO_2$/CO diminishes until at 260° the two oxides are present in approximately equal amounts.

Since the formation of glycol and glycerol involves hydrolysis, it was thought that the addition of water vapour to the reacting medium might increase the yields of both these products; accordingly, a series of experiments was carried out, comparable with the propylene–air series but with the nitrogen replaced by an equivalent quantity of steam. The results are given in Table II.

TABLE II.

*Products from the Reaction of a* 4 : 1 : 3·8-*Propylene–Oxygen–Steam Medium at Various Temperatures between* 240° *and* 280° *and at* 17·6 *Atmospheres Pressure.*

| | % of total oxygen appearing in products as : | | % of oxygen in condensable products appearing as : | | | | |
|---|---|---|---|---|---|---|---|
| Reaction temp. | $CO_2$. | CO. | Total aldehydes. | Total acids. | Propylene oxide and glycol. | Glycerol. | By diff. (mainly $H_2O$). |
| 240° | 22·9 | 7·4 | 14·4 | 8·7 | 4·9 | 6·2 | 65·8 |
| 258 | 23·6 | 13·0 | 26·0 | 3·8 | 7·7 | 6·5 | 56·0 |
| 269 | 43·6 | 16·2 | 35·5 | 9·8 | 19·7 | 11·2 | 23·8 |
| 280 | 35·0 | 10·2 | 33·5 | 6·9 | 10·3 | 14·4 | 34·9 |

The immediate effect of this replacement is to slow down the combustion, and consequently somewhat higher temperatures have to be employed to obtain reaction rates comparable with those of the air series. The general effect is to favour the formation and survival of the initial products of combustion and hydrolysis. For instance, the yield of total aldehydes reaches a maximum of 35·5%, propylene oxide and glycol 19·7%, and glycerol 14·4%. A rapid rate of reaction also seems to favour their survival.

*The Slow Oxidation of Allyl Alcohol and Propylene Glycol.*—The three isomeric compounds (propylene oxide, allyl alcohol, and propaldehyde) which are found in the early stages of propylene oxidation may be formed simultaneously as a result of intermolecular changes from an initially formed propylene–oxygen complex, or they may owe their origin to the specific nature of the oxygen attack, their formation depending upon such factors as the orientation of the reacting molecules at the moment of collision, the concentration of hydrocarbon, and the temperature. Our experiments do not enable a distinction to be drawn between these possibilities. It is easy to show, however, that whereas propylene glycol results from the hydrolysis of the oxide, glycerol is formed solely by the oxidation and hydrolysis of allyl alcohol. For example, a 2 : 5 allyl alcohol–air medium at 14 atm. reacts at 230° and upwards, ignition occurring at 270°. The products consist of aldehydes, acids, glycerol, the two oxides of carbon, and steam; at 235° about 23% of the carbon of the alcohol burnt appears as total aldehydes, and 4% as glycerol. Under similar conditions neither propylene glycol nor propaldehyde gives glycerol, the products of the reaction of the former being aldehydes and acids and those of the latter being peroxide compounds, alcohols, lower aldehydes, and acids (J., 1939, 1717).

*The Slow Oxidation of Ethylene.*—The products from the slow oxidation of ethylene are less numerous than in the case of propylene, and the influence of temperature and pressure on the course of the combustion is easier to determine. A 2 : 1-ethylene–air medium at pressures of 10 atm. and upwards will react at a temperature as low as 200°, giving acetaldehyde and formaldehyde, ethylene glycol, acetic and formic acids, the two oxides of carbon, and steam. In certain circumstances small amounts of methyl and ethyl alcohols, formed by secondary reactions, are also found, but little or no ethylene oxide.

The results of three series of experiments with a 2 : 1 ethylene–air mixture at 30, 68, and 100 atm. and over a temperature range giving at one extremity very slow isothermal combustion and at the other rapid combustion with self-heating, are summarised in Table III.

TABLE III.

*Products from the Reaction of a* 2 : 1-*Ethylene–Air Medium at* 30, 68, *and* 100 *Atm. Pressure and at Various Temperatures.*

| | % of total oxygen appearing in products as : | | % of oxygen in condensable product appearing as : | | | | |
|---|---|---|---|---|---|---|---|
| Reaction temp. | $CO_2$. | CO. | H·CHO. | $CH_3$·CHO. | Ethylene glycol.* | Acetic and formic acids. | By diff. (mainly $H_2O$). |
| | | | Initial pressure : 30 atm. | | | | |
| 237° | 40·8 | 32·0 | 31·6 | 35·6 | 1·5 | 23·6 | 7·7 |
| 246 | 32·3 | 35·8 | 20·2 | 20·0 | 8·7 | 16·8 | 34·3 |
| 276 | 32·5 | 29·1 | 21·8 | 13·8 | 21·0 | 10·3 | 33·1 |
| | | | Initial pressure : 68 atm. | | | | |
| 221 | 31·3 | 37·1 | 9·8 | 4·1 | 8·7 | 56·0 | 21·4 |
| 230 | 31·8 | 19·1 | 4·4 | 3·7 | 7·4 | 31·0 | 53·5 |
| 252 | 28·9 | 25·6 | 4·1 | 9·7 | 18·2 | 15·8 | 52·2 |
| 255 | 26·1 | 31·8 | 6·6 | 15·2 | 13·4 | 21·1 | 43·7 |
| | | | Initial pressure : 100 atm. | | | | |
| 209 | 28·9 | 22·3 | 1·9 | 5·3 | 19·0 | 29·7 | 44·1 |
| 215 | 26·3 | 24·3 | 1·5 | 6·6 | 21·2 | 18·2 | 52·5 |
| 226 | 26·3 | 26·3 | 1·3 | 7·1 | 26·8 | 17·3 | 47;5 |
| 236 | 30·7 | 30·7 | 1·2 | 9·4 | 40·6 | 17·3 | 31·5 |

* Contains only traces of ethylene oxide.

It will be seen that by increasing the initial pressure of the reacting medium the yields of ethylene glycol are increased whilst those of both formaldehyde and acetaldehyde are diminished. The effect of increasing the reaction temperature, at constant pressure, is to increase the yields of glycol and to diminish those of acetic and formic acids. At 30 atm. the yields of the two aldehydes diminish, whereas at higher pressures they tend to increase with increasing temperature. The ratio $CO_2$/CO shows no marked variation with temperature or pressure.

The effect of replacing the nitrogen of the air by steam is shown in Table IV. At 68 atm. the amounts of glycol surviving in the products are considerably increased, whilst the corresponding figures for the acids show a marked diminution. The aldehydes do not appear to be much affected by the substitution of steam. The ratio $CO_2/CO$, which has a value of about unity for the ethylene–air mixtures, increases to 3—4 for the steam-diluted mixtures.

TABLE IV.

*Products from the Reaction of a 9 : 1 : 3·8-Ethylene–Oxygen–Steam Medium at 68 Atm. and at Various Temperatures.*

| Reaction temp. | % of total oxygen appearing as: $CO_2$. | CO. | % of oxygen in condensable products appearing as: H·CHO. | $CH_3$·CHO. | Ethylene glycol.* | Acetic and formic acids. | EtOH. | By diff. (mainly $H_2O$). |
|---|---|---|---|---|---|---|---|---|
| 222° | 49·1 | 13·0 | 6·0 | 9·8 | 20·6 | 18·1 | 12·6 | 32·9 |
| 241 | 36·3 | 8·1 | 6·4 | 4·2 | 17·4 | 5·0 | 9·9 | 57·1 |
| 256 | 37·0 | 10·2 | 3·4 | 4·8 | 18·6 | 4·4 | 6·2 | 62·6 |

* Contains only traces of ethylene oxide.

In all the ethylene experiments some polymerisation of the hydrocarbon to a brownish oil takes place.

*Analytical.*—The methods of identifying and estimating aldehydes, alcohols, and acids have been described in previous papers (Newitt and Thornes, J., 1937, 1656; Newitt and Baxt, J., 1939, 1711).

Ethylene glycol was oxidised by acid potassium permanganate to glyoxal, which was identified by the Bamberger test and by preparing the dinitrobenzoate.

Propaldehyde was oxidised to oxalic acid by means of potassium permanganate, and the acid reduced by zinc and hydrochloric acid to glyoxylic acid. On addition of phenylhydrazine hydrochloride and potassium ferricyanide a red colour is produced (Paget and Berger, *J. Pharm. Chim.*, 1938, **8**, 577; McNair, *J. Amer. Chem. Soc.*, 1932, **54**, 3249).

Ethylene oxide and propylene oxide give a pink precipitate on addition of a saturated, neutral solution of manganese chloride (Lenher, *ibid.*, 1931, **53**, 3737). They were estimated quantitatively by a method due to Lubath (*Chem. and Ind.*, 1932, **51**, 361), which involves the addition of hydrochloric acid to the oxide.

Glycerol was detected by converting it into dihydroxyacetone, which gives a characteristic indigo-blue ring on adding concentrated sulphuric acid and a 1% alcoholic solution of veratrole (Arreguine, *Anal. Asoc. Quím. Argentina*, 1936, 24). Its presence was confirmed by preparing the tribenzoate. The quantitative estimation was carried out by the method described by Malaprade (*Bull. Soc. chim.*, 1937, **4**, 906). The solution containing glycerol was exactly neutralised (pale-yellow tint) with methyl-red as indicator, an excess of sodium periodate solution was added, and the mixture set aside for 20 mins. A concentrated solution of potassium nitrate was added, and the appearance of a white precipitate of potassium periodate indicated the presence of an excess of the sodium salt. The resulting solution, which was acid, as shown by the red colour of the indicator, was titrated against standard sodium hydroxide to the original yellow tint. The reaction is $2NaIO_4 + C_3H_8O_3 = 2H{\cdot}CHO + H{\cdot}CO_2H + 2NaIO_3 + H_2O$, 1 equiv. of glycerol giving 1 equiv. of formic acid.

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## 28. *Trityl Derivatives of Xylofuranose.*

By R. J. MCILROY.

Tritylation of methylxylofuranoside (αβ-mixture) with trityl chloride in pyridine gave 3 : 5-ditrityl methylxyloside. Tritylation followed by acetylation, gave 2 : 3-diacetyl 5-trityl methylxyloside.

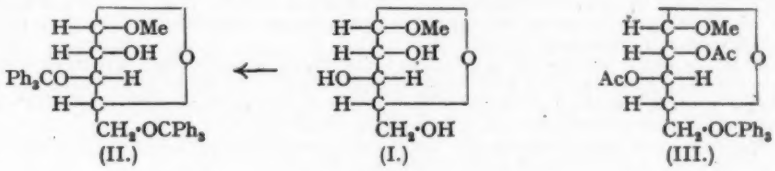
HOCKETT and HUDSON (*J. Amer. Chem. Soc.*, 1931, **53**, 4457) demonstrated that α-methylxyloside, β-methylxyloside, α-methyllyxoside, and β-methylarabinoside reacted with trityl (triphenylmethyl) chloride in pyridine although the primary alcoholic hydroxyl group, normally substituted specifically by this reagent, was engaged in ring formation. Jackson, Hockett, and Hudson (*J. Amer. Chem. Soc.*, 1934, **56**, 947) prepared two crystalline isomeric ditrityl derivatives (m. p. 238—240°, $[\alpha]_D^{20°}$ −55·5° in pyridine, and m. p. 162·5—163°, $[\alpha]_D^{20°}$ −22·5° in pyridine, respectively), and a syrup from β-methylxyloside. Acetylation of the syrup yielded two isomeric crystalline diacetyl monotrityl β-methylxylosides: m. p. 169—170°, $[\alpha]_D^{20°}$ −15·7° in chloroform, and m. p. 125—127°, $[\alpha]_D^{20°}$ −49·1° in chloroform, respectively. Tritylation of xylose (Zeile and Kruckenberg, *Ber.*, 1942, **75**, 1127) gave a mixture of monotrityl xylose (32%) and ditrityl xylose (49%).

It was anticipated that tritylation of methylxylofuranoside (αβ-mixture), in which the primary alcoholic hydroxyl group ($C_5$) is free, would yield a normal 5-trityl derivative and so support the assumption that trityl chloride reacts preferentially with the primary alcoholic hydroxyl group unless that group is engaged in ring formation.

Methylxylofuranoside (αβ-mixture) (I) prepared from xylose by the method of Haworth and Westgarth (*J.*, 1926, 880), when treated with trityl chloride in pyridine for 12 hours at room temperature, followed by 1 hour on a boiling water-bath, yielded crystalline ditrityl methylxylofuranoside (m. p. 78°, $[\alpha]_D^{20°}$ +4·0° in chloroform), identified as 3 : 5-*ditrityl methylxyloside* (II) by methylation to 2-*methyl* 3 : 5-*ditrityl methylxyloside* which, on detritylation and hydrolysis, gave crystalline 2-methyl xylose. Acetylation of tritylated methylxyloside by acetic anhydride in pyridine prior to isolation gave a *diacetyl monotrityl methylxyloside* (III) as an orange glass, $[\alpha]_D^{20°}$ +11·2° in chloroform. The formation of (III) may be explained by the existence of two trityl

derivatives of methylxylofuranoside; namely, 3 : 5-ditrityl methylxylofuranoside and syrupy 5-trityl methylxylofuranoside. It is this latter substance which gives rise to (III).

Methanolysis of the diacetyl monotrityl methylxyloside (III) removed both acetyl and trityl groups leaving methylxyloside which was characterised by methylation to trimethyl methylxyloside and subsequent hydrolysis to crystalline 2 : 3 : 4-trimethyl xylose.




## Experimental.

*Tritylation of Methylxylofuranoside.*—Methylxylofuranoside ($\alpha\beta$-mixture) (6·5 g.) prepared from xylose (B.D.H. reagent) by the method of Haworth and Westgarth (*loc. cit.*) was dissolved in dry, redistilled pyridine (30 c.c., b. p. 118°). Dry trityl chloride (10·7 g., recrystallised from benzene containing 10% acetyl chloride) was added, and the solution, after standing for 12 hours at room temp., was heated for 1 hour with exclusion of moisture on a boiling water-bath. To the clear solution, at 0°, distilled water was added to permanent turbidity and the solution then poured into ice-water (1 l.). After 3 hours the separated orange gum was removed by decantation and washed with water. The gum was dissolved in ether and the ether solution washed with dilute acetic acid, aqueous bicarbonate (3 times) and finally with water. The ether extract, dried over anhydrous sodium sulphate and evaporated under reduced pressure, yielded an orange-red viscous syrup which from solution in absolute alcohol gave colourless prisms (11·9 g.), m. p. 78°, $[\alpha]_D^{20°}$ +4·0° (in chloroform, *c* 1·0) (Found: Trityl, 74·7. $C_{44}H_{40}O_5$ requires trityl 74·99%). (The trityl content was estimated by the method of Valentin, *Coll. Czechoslov. Chem. Comm.*, 1931, **3**, 499.)

2-*Methyl* 3 : 5-*Ditrityl Methylxyloside.*—Ditrityl methylxyloside (5·0 g.) dissolved in methyl iodide (16 c.c.) was refluxed for 8 hours at 45°, silver oxide (8 g.) being added in 1 g. portions at hourly intervals. After evaporation under reduced pressure, the *methylated product* was extracted with chloroform and the solvent evaporated, yielding 5·2 g. of syrup, $[\alpha]_D^{16°}$ + 6° (in chloroform, *c* 0·72) (Found: OMe, 9·0. $C_{45}H_{42}O_5$ requires OMe, 9·0%).

*Detritylation of methyl ditrityl methylxyloside.* Methyl ditrityl methylxyloside (2·8 g.) was refluxed with methanolic hydrogen chloride (50 c.c., containing 1·5% HCl) for 2 hours at 95°. The solution was neutralised by silver carbonate, filtered, and the filtrate evaporated at 40° under reduced pressure. The residue was extracted exhaustively with warm water and the aqueous extracts were evaporated and extracted with chloroform. Evaporation of the chloroform gave monomethyl methylxyloside (0·53 g.) as a golden brown syrup (Found: OMe, 35·0. Calc. for $C_7H_{14}O_5$: OMe, 34·83%).

*Hydrolysis of methyl methylxyloside.* The methyl methylxyloside (0·52 g.) was hydrolysed by 2% nitric acid (52 c.c.) at 95°, the hydrolysis being followed polarimetrically: $[\alpha]_D^{19°}$ +55° (30 min.); +36° (90 min.); +36° (120 min., *c* 1·0). The solution was neutralised by barium carbonate, filtered, the filtrate evaporated at 40° and exhaustively extracted with boiling acetone and boiling ether. Evaporation of the solvent gave 2-methyl xylose (0·42 g.), m. p. 131—132° (from ethyl acetate), $[\alpha]_D^{20°}$ +36° (in water, *c* 1·0) (Found: OMe, 18·6. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). Cf. 2-methyl xylose, m. p. 132—133°, $[\alpha]_D^{20°}$ +35·9° in water (Robertson and Speedie, *J.*, 1934, 824).

2 : 3-*Diacetyl* 5-*Trityl Methylxyloside.*—To methyl xylofuranoside ($\alpha\beta$-mixture) (10·0 g.) dissolved in dry pyridine (50 c.c.; b. p. 118°), dry trityl chloride (17 g.) was added. After standing for 12 hours at room temp. the solution was heated 1 hour on a boiling water-bath and allowed to cool. Acetic anhydride (50 c.c.) was added and the solution left at room temp. for a further 24 hours. The mass of white crystals (4·12 g.) was removed by filtration, washed with pyridine and then with distilled water, the pyridine washings being added to the mother-liquor. The crystals were identified as triphenylmethylcarbinol, m. p. 158°. Distilled water was added, to the mother-liquor cooled to 0°, to permanent turbidity. On pouring the solution into ice water (1·5 l.) a creamy gummy material separated; this was removed by decantation, washed thoroughly with water, dissolved in ether and the ether solution washed with aqueous sodium bicarbonate (three times), then with water till free from acid, and dried over anhydrous sodium sulphate. Evaporation of the ether yielded an orange glass (23·7 g.), $[\alpha]_D^{20°}$ +11·2° (in chloroform, *c* 0·85) (Found: OMe, 6·3; trityl, 49·4. $C_{29}H_{30}O_7$ requires OMe, 6·3; trityl 49·6%).

*Conversion of diacetyl monotrityl methylxyloside to trimethyl xylose.* Diacetyl monotrityl methylxyloside (23·6 g.) was refluxed for 3½ hours at 95° with methanol (100 g.) containing hydrogen chloride (3 g.), the solution neutralised by silver carbonate, filtered, and the filtrate evaporated to dryness under reduced pressure. The residue was extracted with warm water, the aqueous extracts being evaporated under reduced pressure to give methylxylopyranoside as an impure syrup (6·85 g.) (Found: OMe, 17·8. Calc. for $C_7H_{14}O_5$: OMe, 18·9%). The impure methylxylopyranoside (6·75 g.) was twice methylated with methyl iodide (70 c.c.) and silver oxide (35 g.) during 10 hour periods at 45°. The methylated product, a mobile yellow syrup (7·93 g.), isolated in the usual way, consisted mainly of a mixture of $\alpha$ and $\beta$ forms of trimethyl methylxylopyranoside, $n_D^{21°}$ 1·4410, $[\alpha]_D^{18°}$ +55·1° (in methyl alcohol, *c* 0·99) (Found: OMe, 55·3%. Calc. for $C_9H_{18}O_5$: OMe, 60·2%). Distillation gave a colourless syrup (6·32 g.), $n_D^{17°}$ 1·441, b. p. 125—130° (bath temp.)/17 mm., $[\alpha]_D^{18°}$ +57·0° (in methanol, *c* 1·07). The trimethyl methylxyloside (6·32 g.) was hydrolysed by 2% nitric acid (70 c.c.) for 2 hours at 95°, neutralised by barium carbonate, filtered, and the filtrate evaporated under reduced pressure. Extraction of the residue with boiling acetone and boiling ether and evaporation of the solvents gave a colourless syrup (5·5 g.) which slowly deposited crystals of trimethyl xylose, m. p. 88—89°, $[\alpha]_D^{20°}$ +19·8° at equilibrium (in water, *c* 0·86) (Found: OMe, 48·0; C, 49·9; H, 8·4. Calc. for $C_8H_{16}O_5$: OMe, 48·4; C, 50·0; H, 8·3%). $[\alpha]_D^{17°}$ +20·4° in water (equilibrium value); Haworth and Percival, *J.*, 1931, 2850, give m. p. 90—92°.

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## 29. *Synthesis of Diaminoacridines. Part I.*

By Alan A. Goldberg and William Kelly

Various routes to 2 : 7-diaminoacridone have been investigated and three new syntheses described :* *viz.*, (i) condensation of the 4-nitro- or 4-acetamido- derivative of 2-chlorobenzoic acid with *p*-phenylenediamine or *p*-aminoacetanilide followed by *cyclo*dehydration, (ii) condensation of the 5-nitro- or 5-acetamido-derivative of 2-chlorobenzoic acid with *m*-phenylenediamine with subsequent *cyclo*dehydration and (iii) nitration of 2-nitroacridone, followed by reduction.

A number of 3′-nitro- and 3′-amino-diphenylamine-2-carboxylic acids bearing a further substituent in the carboxylated nucleus have been cyclised with sulphuric acid and in all cases it has been shown that in the 3′-nitro series ring closure takes place principally on the 2′-position (*ortho*-closure) and in the 3′-amino series cyclisation takes place almost exclusively on the 6′-position (*para*-closure).

General observations have been made on the influence of substituents in the carboxylated nucleus upon the ease of cyclisation of monosubstituted diphenylamine-2-carboxylic acids.

2 : 7-Diaminoacridine has been shown to possess high antibacterial activity and comparatively low tissue and systemic toxicity together with physical properties which recommend its use as a general antiseptic in place of proflavine (Albert, Dyer, and Linnell, *Quart. J. Pharm.*, 1937, **10**, 649; Ungar and Robinson, *J. Pharm. Exp. Ther.*, 1944, **80**, 217). The method reported for the preparation of the compound (Albert and Linnell, *J.*, 1936, 1614) leaves much to be desired because the intermediate compound, 5 : 4′-dinitrodiphenylamine-2-carboxylic acid, is difficult of access; it was accordingly thought desirable to investigate alternative synthetic routes.

The general literature relating to the Ullmann condensation between negatively substituted arylamines and 2-halogenobenzoic acids (Ullmann, *Annalen*, 1907, **355**, 312; Tuttle, *J. Amer. Chem. Soc.*, 1923, **45**, 1906; Bogert and Hirschfelder, *Coll. Trav. Chim. Czeckoslov.*, 1930, **5/6**, 382; Magidson and Trawin, *Ber.*, 1936, **69**, 537; Albert and Linnell, *J.*, 1936, 89 and 1614; Lehmstedt and Schrader, *Ber.*, 1937, **70**, 838) indicates that the presence of a negative substituent in either of the reactants, particularly in the arylamine nucleus, exerts an inhibiting influence upon the course of the condensation; attention was directed, therefore, to the interaction of the corresponding positively substituted arylamine with the negatively and with the positively substituted 2-halogenobenzoic acid. It was found that *p*-phenylenediamine readily reacts with 2-chloro-4-nitrobenzoic acid but under the usual conditions of the Ullmann reaction, *viz.* at *ca.* 140° in amyl alcohol, the diamine effects reductive dehalogenation of the chloronitrobenzoic acid with formation of *p*-nitrobenzoic acid in almost quantitative yield. At *ca.* 80°, however, in *iso*propyl alcohol, the normal Ullmann reaction takes place smoothly with production of *5-nitro-4′-aminodiphenylamine-2-carboxylic acid* in satisfactory yield; even at this abnormally lowered temperature appreciable amounts of *p*-nitrobenzoic acid are formed. At 100°, 120°, and 130° in amyl alcohol the ratios at which the normal Ullmann reaction and the reductive dehalogenation take place are approximately 60 : 40, 40 : 60, and 20 : 80 respectively. Similarly at 140°, *p*-aminodimethylaniline reacts vigorously with 2-chloro-4-nitrobenzoic acid with formation of *p*-nitrobenzoic acid, but the tendency to effect reductive dehalogenation would appear to be less than with *p*-phenylenediamine since, at 120°, a high yield of *5-nitro-4′-dimethylaminodiphenylamine-2-carboxylic acid* is obtainable. Interaction of *p*-phenylenediamine with 2-chloro-4-acetamidobenzoic acid gave analogous results; at 140° *p*-acetamidobenzoic acid is the principal product while at 100° the desired *4′-amino-5-acetamidodiphenylamine-2-carboxylic* acid is obtained in satisfactory yield.

Monoacylation of the diamine was found to inhibit the ability of the latter to effect dehalogenation; 2-chloro-4-acetamidobenzoic acid condenses smoothly with *p*-aminoacetanilide and even at elevated temperatures 5 : 4′-*di*(*acetamido*)*diphenylamine-2-carboxylic* acid is the sole reaction product. It is believed that the reductive dehalogenation (hydrogenolysis) of activated halogeno-aryls (compare Lehmstedt, *Ber.*, 1937, **70**, 1526) may serve as a useful method for obtaining the corresponding nonhalogenated aryl where other methods fail or cannot be employed (also compare the use of Raney nickel for this purpose, Schwenk *et al.*, *J. Org. Chem.*, 1944, **9**, 1).

An alternative route to 2 : 7-diaminoacridone is evidently available from suitable 4 : 3′-disubstituted diphenylamine-2-carboxylic acids provided that closure of the acridone ring can be effected at the 6′-position. Accordingly 2-chloro-5-nitrobenzoic acid was condensed with *m*-nitroaniline and with *m*-phenylenediamine to give 4 : 3′-dinitro- and *4-nitro-3′-aminodiphenylamine-2-carboxylic* acids respectively; in addition 2-chloro-5-acetamidobenzoic acid and *m*-phenylenediamine gave *3′-amino-4-acetamidodiphenylamine-2-carboxylic acid* in excellent yield. In this series, *i.e.* 5-substituted 2-chlorobenzoic acids, there appeared to be little tendency to undergo hydrogenolysis on treatment with the diamine and the temperature of the reaction accordingly is not critical.

2-Chloro-3-acetamidobenzoic acid failed to condense with aniline and *m*-phenylenediamine; under all the conditions used, from 100° to 140°, dehalogenation of the chloroacetamidobenzoic acid took place with formation of *m*-acetamidobenzoic acid. *m*-Nitroaniline similarly effected dehalogenation at 140°, and at 100° no reaction was observable. 2-Chloro-3-nitrobenzoic acid, however, condensed smoothly with aniline to yield *6-nitrodiphenylamine-2-carboxylic acid.*

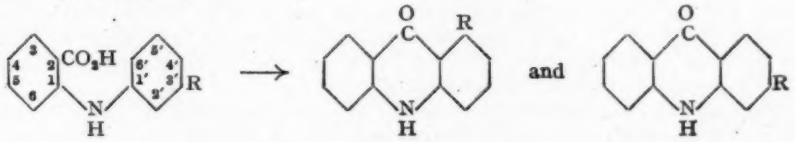
2-Chloro-6-acetamidobenzoic acid and 2-chloro-6-nitrobenzoic acid condensed with aniline to give

* British and U.S. Patent Specifications pending.

*3-acetamidodiphenylamine-2-carboxylic acid* and *3-nitrodiphenylamine-2-carboxylic acid* respectively. The results of the condensation of the 3-acetamido- and the 3-nitro-derivative of 2-chlorobenzoic acid and of the 6-acetamido- and the 6-nitro-derivative of 2-chlorobenzoic acid with *m*-nitroaniline and *m*-phenylenediamine will be reported shortly.

cyclo*Dehydration of Substituted Diphenylamine-2-carboxylic Acids.*—Treatment of 5-nitro-4′-aminodiphenylamine-2-carboxylic acid with hot sulphuric acid (Jourdan, *Ber.*, 1885, **18**, 1444; Ullmann, *loc. cit.*) effected cyclisation with formation of *2-nitro-7-aminoacridone* which on reduction yielded 2 : 7-diaminoacridone. Similarly, cyclisation and simultaneous hydrolysis of 5 : 4′-di(acetamido)diphenylamine-2-carboxylic acid gave 2 : 7-diaminoacridone and both of these methods constitute facile routes to the latter.

While 2′- and 4′-substituted diphenylamine-2-carboxylic acids can undergo cyclisation with formation in each case of only one product, the 3′-substituted diphenylamine-2-carboxylic acids may give rise to 4- or 2-substituted acridones according to whether the acridone ring closes on the 2′-position (*ortho*-closure) or the 6′-position (*para*-closure) respectively.




*ortho*-closure *para*-closure

Thus both the 2 : 6- and the 2 : 8-dinitro-derivative of 5-chloroacridine are simultaneously formed by the action of phosphoryl chloride on 5 : 3′-dinitrodiphenylamine-2-carboxylic acid (Albert and Linnell, *J.*, 1936, 89). Lehmstedt and Schrader (*Ber.*, 1937, **70**, 838) made quantitative measurements upon the directional cyclisation of a series of 3′-substituted diphenylamine-2-carboxylic acids and reported that the ratio of *ortho*- to *para*-closure is 75 : 25 when the 3′-substituent is $NO_2$ (negative) and 20 : 80 when the 3′-substituent is Me (positive). These authors believed that the same or a similar ratio would obtain with a 3′-amino substituent as with a 3′-nitro substituent but, later, this assumption was shown to be incorrect as 2- and 4-aminoacridones were obtained in the ration of *ca.* 8 : 1 by the cyclisation of 3′-aminodiphenylamine-2-carboxylic acid (Albert and Ritchie, *J.S.C.I.*, 1941, **60**, 120), *i.e.* *para*-closure largely predominates. The present work relates to the *cyclo*-dehydration of 3′-nitro- and 3′-amino-diphenylamine-2-carboxylic acids which have another substituent in the carboxylated nucleus and in all cases it has been shown that, while with the 3′-nitro- series *ortho*-closure largely predominates, with the 3′-amino- series *para*-closure takes place almost exclusively. Thus 3′-nitro-4-acetamidodiphenylamine-2-carboxylic acid yields principally 6-nitro-3-aminoacridone which on reduction gives 3 : 6-diaminoacridone, m. p. 314—316°, and 3 : 6-diaminoacridine, m. p. 254—256°; the constitution of the latter (not previously proved) was shown by its identity with the diaminoacridine obtained by nitration of 4-nitroacridone and reduction of the dinitroacridone thus obtained. On the other hand cyclisation of 3′-amino-4-acetamidodiphenylamine-2-carboxylic acid takes place with almost exclusive formation of 2 : 7-diaminoacridone, m. p. 358—360°, which on reduction yields 2 : 7-diaminoacridine identical with the diaminoacridine obtained by the nitration of 2-nitroacridone and reduction of the resulting dinitroacridone.

Similarly 3′ : 4-dinitro-diphenylamine-2-carboxylic acid cyclises into 3 : 6-dinitroacridone which on reduction gives 3 : 6-diaminoacridone, m. p. 314—316° (compare Albert and Linnell, *J.*, 1938, 22) whereas *cyclo*dehydration of 4-nitro-3′-aminodiphenylamine-2-carboxylic acid yields *7-nitro-2-aminoacridone* which on reduction gives 2 : 7-diaminoacridone, m. p. 358—360°.

In the same manner 3′-nitro-5-acetamidodiphenylamine-2-carboxylic acid yields 6-nitro-2-aminoacridone which on reduction gives successively 2 : 6-diaminoacridone, m. p. 304—306°, and 2 : 6-diaminoacridine, m. p. 204—206°, while 3′-amino-5-acetamido-diphenylamine-2-carboxylic acid yields almost exclusively 2 : 8-diaminoacridone, m. p. 368—370°, which on reduction gives 2 : 8-diaminoacridine, m. p. 284—286°. Similarly, while 3′ : 5-dinitro-diphenylamine-2-carboxylic acid yields 2 : 6-dinitroacridone which on reduction leads to 2 : 6-diaminoacridone, m. p. 300—302°, and 2 : 6-diaminoacridine, m. p. 204—206°, 5-nitro-3′-amino-diphenylamine-2-carboxylic acid gives principally 8-nitro-2-aminoacridone which on reduction is convertible into 2 : 8-diaminoacridone, m. p. 366—368°, and 2 : 8-diaminoacridine, m. p. 284—286°.

The *cyclo*dehydration of diphenylamine-2-carboxylic acid bearing a single substituent in the carboxylated nucleus presents several anomalies. Diphenylamine-2-carboxylic acid itself readily undergoes cyclisation with sulphuric acid at 90—100° yielding in 30 minutes and 120 minutes almost quantitative yields of acridone and acridone-3-sulphonic acid respectively (Matsumura, *J. Amer. Chem. Soc.*, 1935, **57**, 1533); it has been found that avoidance of sulphonation may best be effected by the prolonged action of 70—75% sulphuric acid.* Ullmann (*loc. cit.*) failed to obtain 2-nitroacridone from 5-nitrodiphenylamine-2-carboxylic acid by the use of sulphuric acid and effected cyclisation with aluminium chloride and phosphorus pentachloride (compare also Albert and Linnell, *loc. cit.*). Repeated attempts to obtain 2- and 3-nitroacridones by the ring closure of 5- and 4-nitrodiphenylamine-2-carboxylic acids were unsuccessful, the only products isolated being nitroacridone-sulphonic acids; this would accord with the observations of Matsumura (*loc. cit.*) who obtained 2-nitroacridone-

* The "concentrated sulphuric acid" (Cohen, "Practical Organic Chemistry" (1930), p. 278) is evidently a mistranslation of "englische Schwefelsäure" from Graebe and Lagodzinski (*Ber.*, 1892, **25**, 1737).

7-sulphonic acid by the action of cold 20% fuming sulphuric acid on 5-nitrodiphenylamine-2-carboxylic acid. Similarly 4-acetamidodiphenylamine-2-carboxylic acid could not be converted into 3-aminoacridone, the only identifiable product being an aminoacridonesulphonic acid, presumably the 3 : 7-isomeride. On the other hand, 6-nitro-diphenylamine-2-carboxylic acid on treatment with sulphuric acid at 100° readily gave 1-nitroacridone which on reduction yielded 1-aminoacridone, whereas 6-acetamidodiphenylamine-2-carboxylic acid suffered almost total decarboxylation on treatment with the cyclising reagent. 3-Acetamidodiphenylamine-2-carboxylic acid gave 4-aminoacridone although in very small yield (*ca.* 5%); 3-nitrodiphenylamine-2-carboxylic acid could not be converted into 4-nitroacridone owing to loss of carbon dioxide. The formation of 1- and 4-aminoacridones from substituted 2-halogenobenzoic acids and aniline has not previously been recorded.

It would appear that substituents in the carboxylated nucleus may, according to their nature and orientation, deactivate the carboxyl group towards cyclisation or, alternatively, they activate the 7-(or 3-)position of the acridone first obtained and thus facilitate sulphonation in this position. This accords with the successful closure of 4′-substituted diphenylamine-2-carboxylic acids in which the activated 7-(or 3-)position is blocked and also of 3′-nitrodiphenylamine-2-carboxylic acids in which the presence of the nitro group would preclude easy sulphonation; but it does not explain the normal cyclisation of 3′-amino-4- and -5-acetamidodiphenylamine-2-carboxylic acids in which the presence of the amino group in the 8-(or 2-)position of the formed acridone would be expected to assist sulphonation at the 7-(or 3-)position.

Since the 3- and 7-positions in the acridone molecule are the predominantly activated positions towards nitrating and sulphonating agents while the 1- and the 9-positions are activated to a far lesser extent (Lehmstedt *et al.*, *Z. angew. Chem.*, 1928, **41**, 220; *Ber.*, 1927, **60**, 1370; 1931, **64**, 1232; 1931, **64**, 2381, 2386; Jensen, *J. Amer. Chem. Soc.*, 1927, **49**, 1049; Scherlin *et al.*, *Annalen*, 1935, **516**, 218; Matsumura, *J. Amer. Chem. Soc.*, 1935, **57**, 1533; 1938, **60**, 593) the possibility presented itself that 2 : 7-dinitroacridone could be obtained by the nitration of the easily accessible 2-nitroacridone. It was found that the latter nitrates smoothly in sulphuric acid solution with production of 2 : 7-dinitroacridone in almost theoretical yield; no 2 : 9-dinitroacridone could be separated from the crude reaction product. Reduction with stannous chloride effected quantitative formation of 2 : 7-diaminoacridone and further reduction of the crude diaminoacridone with sodium amalgam followed by oxidation of the resulting diaminoacridane gave 2 : 7-diaminoacridine in good yield. Since the m. p. of the crude product, 348—352°, was very little different from that of the recrystallised material, 354—356°, this is additional evidence for the absence of any but traces of the isomeric 2 : 9-dinitroacridone in the crude nitration product (2 : 9-diaminoacridine has m. p. 250°). This would appear to be the easiest method of preparing 2 : 7-diaminoacridine. Similarly, nitration of 4-nitroacridone yielded 3 : 6-dinitroacridone which was successively converted into 3 : 6-diaminoacridone and 3 : 6-diaminoacridine. The identity of the m. p. of the latter (254—256°) with that of the product obtained by the cyclisation of 3′ : 4-dinitrodiphenylamine-2-carboxylic acid followed by reduction (254—256°) would indicate that the m. p. of 322° for this compound given by Albert and Linnell (*loc. cit.*) is incorrect.

Cyclisation of 5-nitro-4′-dimethylaminodiphenylamine-2-carboxylic acid by the phosphoryl chloride method (Lesnianski, *Bull. Acad. Polonaise*, 1929, A, 81; Magidson and Grigorowski, *Ber.*, 1933, **66**, 866; Borsche, Runge, and Trautner, *ibid.*, 1933, **66**, 1315; Dirscherl and Thron, *Annalen*, 1933, **504**, 297) gave *5-chloro-2-nitro-7-dimethylaminoacridine* which on acid hydrolysis yielded *2-nitro-7-dimethylaminoacridone*; reduction of the latter with stannous chloride gave *2-amino-7-dimethylaminoacridone* which was converted by sodium amalgam followed by oxygenation into *2-amino-7-dimethylaminoacridine*.

4′-Dimethylamino- and 5-chloro-4′-dimethylamino-diphenylamine-2-carboxylic acids on cyclisation with phosphoryl chloride afforded in good yield 5-chloro-3-dimethylamino- and 5 : 8-dichloro-3-dimethylaminoacridine respectively. The presence of the 3-dimethylamino substituent exerts a strong stabilising influence upon the *meso*-halogen since both these compounds may be recrystallised without decomposition from boiling aqueous alcohol whereas 5-chloroacridine under similar conditions is rapidly converted into acridone (compare also the stabilisation of *meso*-halogens by a 3-methoxy group). 5-Chloro-3-dimethylamino- and 5 : 8-dichloro-3-dimethylamino-acridine reacted readily with ammonium carbonate in phenol solution with formation of *5-amino-3-dimethylamino-* and *8-chloro-5-amino-3-dimethylamino-acridine* respectively; both these diamines possess powerful antibacterial activity and low tinctorial values.

## Experimental.

All m. ps. above 310° were determined on a Mason's block, the compound being inserted at *ca.* 20° below its m. p. All compounds for analysis were dried at 100—110°/1 mm. over phosphoric oxide.

*General Procedure used for Ullmann Reactions.*—The 2-halogenobenzoic acid was dissolved in 4 to 10 times its weight of rectified amyl alcohol (b. p. 132—136°), potassium carbonate added and the mixture stirred rapidly at the boiling point for ½ hour during which time *ca.* one-tenth of the solvent was allowed to distil off in order to remove most of the water and obtain the potassium salt of the acid in a voluminous state. The mixture was cooled, the arylamine and copper catalyst added and the stirring continued at the stated temperatures; the amyl alcohol was removed by distillation in steam, the residual liquid filtered from neutral material and whilst stirred at 80—100° adjusted to pH 4 with 5N-hydrochloric acid. The precipitated diphenylaminecarboxylic acid collected from the hot solution was usually purified by dissolution in a large volume of boiling water containing a slight excess of ammonia and the free acid reprecipitated from this boiling, *ca.* 5%, solution of the ammonium salt by adjustment to *p*H 4 and collection at the boiling point. This procedure effectively removed unchanged halogenobenzoic acids and by-products (*e.g.*, *p*-nitrobenzoic acid) with little loss of product. In some cases, particularly with nitrodiphenylamine-2-carboxylic acids, crystallisation of the potassium salt was found to be effective and economical. Formation of the diphenylaminecarboxylic acid in high yield, particularly when the reaction is conducted at low temperatures, appears to depend to a considerable extent upon

the physical state of the potassium salt of the halogenobenzoic acid and also upon the presence of a trace of water; a voluminous crystalline form of the potassium salt conduces to high yield and this is best obtained by the employment of amyl alcohol containing *ca.* 3% of water and then distilling off most of this water, together with that formed during the neutralisation, before the addition of the arylamine and the catalyst. For example, on three occasions when preformed anhydrous potassium 2-chloro-4-nitro-benzoate, ignited potassium carbonate and anhydrous amyl alcohol were stirred for 4 hours at 120° with *p*-phenylenediamine no reaction took place, the whole of the chloronitrobenzoic acid being recovered unchanged. In many cases the diphenylamine-2-carboxylic acids obtained were too highly coloured or too insoluble in aqueous alcohol for determination of their equivalents.

*Series Derived from 4-Substituted 2-Chlorobenzoic Acids.*

*3'-Amino-5-acetamidodiphenylamine-2-carboxylic Acid.*—2-Chloro-4-acetamidobenzoic acid (10 g.), potassium carbonate (7·5 g.), copper powder (0·2 g.), *m*-phenylenediamine (8 g.) and amyl alcohol (40 c.c.) were stirred at 150° (bath-temperature) for 1 hour. The crude *3'-amino-5-acetamidodiphenylamine-2-carboxylic acid* thus obtained (5·6 g.), m. p. 182—186°, was difficult to purify and was used as such (Found: N, 14·3. $C_{15}H_{15}O_3N_3$ requires N, 14·7%).

2 : 8-*Diaminoacridone.*—The foregoing material (2·6 g.) was dissolved in sulphuric acid (18 c.c.) and the solution heated to 100° for 1½ hours; water (10 c.c.) was added, the heating at 100° continued for a further ½ hour, the solution poured on to ice (100 g.) and basified with aqueous ammonia. Collection of the yellow precipitate and recrystallisation from aqueous pyridine gave 2 : 8-diaminoacridone (0·85 g.) in yellow needles, m. p. 368—370°. The identity of this product was established by reduction with sodium amalgam to 2 : 8-diaminoacridine (proflavine), m. p. 282—284° alone and in admixture with authentic material (Found: N, 20·3. Calc. for $C_{13}H_{11}N_3$: N, 20·1%).

*3'-Nitro-5-acetamido-diphenylamine-2-carboxylic Acid.*—2-Chloro-4-acetamidobenzoic acid (10 g.), *m*-nitroaniline (8 g.), potassium carbonate (7 g.), copper powder (0·2 g.) and amyl alcohol (40 c.c.) were stirred at 150° (bath temperature) for 2½ hours. The crude product, after extraction three times with boiling water (300 c.c. each time), was recrystallised from aqueous alcohol and gave *3'-nitro-5-acetamidodiphenylamine-2-carboxylic acid* (6·2 g.) in yellow needles, m. p. 246—248° (Found: N, 13·3; *M*, by titration, 315. $C_{15}H_{13}O_5N_3$ requires N, 13·3%; *M*, 315).

2 : 6-*Diaminoacridone.*—The foregoing acid (6 g.) dissolved in sulphuric acid (45 c.c.) was heated to 100° for 1½ hours, water (15 c.c.) added, the solution heated at this temperature for a further ½ hour and poured on to ice (200 g.). The precipitate was collected, ground with aqueous ammonia and washed with hot water, *6-nitro-2-aminoacridone* (4·5 g.) being obtained as a dark powder, m. p. 352—356°. Recrystallisation from aqueous pyridine gave the pure compound in brown-yellow needles, m. p. 366—368° (Found: N, 16·9. $C_{13}H_9O_3N_3$ requires N, 16·5%).

The crude compound (3·5 g.) was added to a solution of stannous chloride crystals (40 g.) in hydrochloric acid (40 c.c.) and the solution heated on the water bath for 2½ hours. After cooling, the mixture was diluted with water (200 c.c.), poured into an excess of 5N-sodium hydroxide, the precipitate collected, redissolved in dilute hydrochloric acid, filtered (charcoal) and basified with 5N-sodium hydroxide. The yellow precipitate was collected and washed with water, 2 : 6-diaminoacridone being obtained (2·5 g.), m. p. 304—306° (sintering at 294°). Recrystallisation from aqueous pyridine gave the pure compound in yellow needles, m. p. 302—304° (lit. 306°) (Found: N, 18·3. Calc. for $C_{13}H_{11}ON_3$: N, 18·7%).

Reduction of the crude diaminoacridone with sodium amalgam gave 2 : 6-diaminoacridine which was obtained in brown needles from aqueous pyridine, m. p. 205—206° (Albert and Linnell, J., 1936, 89, give m. p. 213—216°) (Found: C, 74·1; H, 5·3; N, 20·1. Calc. for $C_{13}H_{11}N_3$: C, 74·6; H, 5·3; N, 20·1%).

*4'-Amino-5-acetamidodiphenylamine-2-carboxylic Acid.*—2-Chloro-4-acetamidobenzoic acid (10 g.), potassium carbonate (7·5 g.), copper powder (0·2 g.), *p*-phenylenediamine (8 g.) and amyl alcohol (40 c.c.) were stirred at 110° (bath temperature, *ca.* 100° internal temperature) for 2½ hours. The crude 4'-amino-5-acetamidodiphenylamine-2-carboxylic acid (5·1 g.), which had m. p. 214° (sintering at 194°), could not be effectively purified; acetylation with acetic anhydride in dilute aqueous sodium carbonate solution (see below) gave *4' : 5-di(acetamido)diphenylamine-2-carboxylic acid* which crystallised from aqueous alcohol in brown needles, m. p. 244—246° (Found: N, 12·7; *M*, by titration, 334. $C_{17}H_{17}O_4N_3$ requires N, 12·9%; *M*, 327).

2 : 7-*Diaminoacridone.*—Crude 4'-amino-5-acetamidodiphenylamine-2-carboxylic acid (4·2 g.) was heated to 100° with sulphuric acid (30 c.c.) for 1 hour, the solution cooled, water (10 c.c.) added, the solution reheated at this temperature for a further ½ hour and poured on to ice (250 g.). After basification with ammonia, the insoluble material was collected and purified by dissolution in dilute hydrochloric acid and reprecipitation with ammonia, 2 : 7-diaminoacridone being obtained (1·7 g.) as a yellow powder, m. p. 340—344°. Recrystallisation from dilute pyridine gave the pure compound in golden-brown plates, m. p. 358—360° (Found: N, 18·7. Calc. for $C_{13}H_{11}ON_3$: N, 18·7%).

*5-Nitro-4-aminodiphenylamine-2-carboxylic Acid.*—2-Chloro-4-nitrobenzoic acid (40 g.) was dissolved in *iso*propyl alcohol (325 c.c.) and potassium carbonate (40 g.) slowly added; after the addition of benzene (75 c.c.), the mixture was stirred and 150 c.c. of the ternary liquid distilled off, leaving the potassium salt as a voluminous crystalline precipitate. Copper powder (1 g.) and *p*-phenylenediamine (27 g.) were added, the mixture stirred whilst gently refluxed (internal temperature 79°) for 7 hours and then distilled in steam. The residual solution was filtered (charcoal) from insoluble black material (10 g.), the filtrate (vol. 750 c.c.) whilst being stirred at the boiling point adjusted to pH 4·0—4·5 with hydrochloric acid, the ochre microcrystalline precipitate of 5-nitro-4'-aminodiphenylamine-2-carboxylic acid (32 g.) collected from the hot liquor, washed with hot water and dried. It had m. p. 264—266° (decomp. with softening at 258°). Acidification of the cold filtrate (750 c.c.) with excess of hydrochloric acid precipitated crude *p*-nitrobenzoic acid which, after dissolution in dilute aqueous ammonia, filtering (charcoal) and reprecipitating with hydrochloric acid and recrystallisation from dilute alcohol, yielded pure *p*-nitrobenzoic acid (10 g.), m. p. and mixed m. p. 242—244° (Found: N, 8·5; *M*, 166. Calc.: N, 8·4%; *M*, 166). The crude nitro-aminodiphenylamine-2-carboxylic acid could not be purified by crystallisation. A sample (8 g.) was dissolved in boiling water (100 c.c.) and potassium carbonate (2·2 g.) and the filtered solution (charcoal) allowed to stand on ice overnight; the potassium salt (glistening crystals) was collected, dissolved in boiling water and the free acid precipitated with hydrochloric acid, pure *5-nitro-4'-aminodiphenylamine-2-carboxylic acid* (3·6 g.) being obtained as a light yellow crystalline powder, m. p. 282—284° (decomp.) (Found: C, 57·0; H, 4·2; N, 15·2. $C_{13}H_{11}O_4N_3$ requires C, 57·1; H, 4·0; N, 15·4%). The filtrate from the collection of the potassium salt gave the less pure acid (3·4 g.), m. p. 256—258° decomp. with softening at 252°.

*Interaction between 2-chloro-4-nitrobenzoic acid and p-phenylenediamine at higher temperatures.* 2-Chloro-4-nitrobenzoic acid (41 g.), potassium carbonate (31 g.), copper powder (1 g.), *p*-phenylenediamine (27 g.), amyl alcohol (390 c.c.) and water (5 c.c.) were submitted to the usual procedure at 130° (internal) for 4½ hours. The crude acid (40 g.), isolated by adjusting the cold liquor to pH 3 after the steam distillation, was purified by repeated precipitation at pH 4·0—4·5 of the boiling (*ca.* 5%) solution of the ammonium salt. This yielded 5-nitro-4'-amino-diphenylamine-2-carboxylic acid still contaminated with *p*-nitrobenzoic acid; the latter was removed by extraction with hot 80% alcohol in which the former is sparingly soluble. The residue (8·5 g.) gave, on crystallisation of the potassium salt and reprecipitation, pure 5-nitro-4'-amino-diphenylamine-2-carboxylic acid (5 g.), m. p. 282—284° (decomp.). The liquors from the

precipitation of the acid at pH 4·0—4·5 were combined, chilled, strongly acidified and the impure *p*-nitrobenzoic acid collected; this was treated with chromic acid in boiling acetic acid solution and yielded, on recrystallisation, pure *p*-nitrobenzoic acid (20 g.), m. p. and mixed m. p. 242—244° (Found: *M*, 166. Calc.: *M*, 166).

When the reaction was carried out for 3 hours at 120° (internal), 5-nitro-4′-amino-diphenylamine-2-carboxylic acid (15·5 g.), m. p. 266—270°, and pure *p*-nitrobenzoic acid (16 g.), m. p. 242—244° (Found: *M*, 167), were obtained. When the reaction was carried out at 100° (internal) for 5 hours, 5-nitro-4′-amino-diphenylamine-2-carboxylic acid (25 g.), m. p. 262—264°, and pure *p*-nitrobenzoic acid (13·5 g.) were obtained.

In three experiments in which preformed anhydrous finely ground potassium 2-chloro-4-nitrobenzoate (48 g.), ignited potassium carbonate (14·7 g.), *p*-phenylenediamine (27 g.), copper powder (1 g.) and anhydrous amyl alcohol (300 c.c.) were stirred at 120° (internal) for 5 hours, unchanged 2-chloro-4-nitrobenzoic acid (30—33 g.), m. p. and mixed m. p. 142—144°, was recovered (Found: Cl, 17·5; *M*, by titration, 201. Calc.: Cl, 17·6%; *M*, 201·5).

*2-Nitro-7-aminoacridone and 2:7-Diaminoacridone.*—Crude 5-nitro-4′-amino-diphenylamine-2-carboxylic acid (25 g.) was dissolved in sulphuric acid (250 c.c.), the solution heated at 100° for 2 hours and poured on to crushed ice (1200 g.). After 2 hours, the pasty yellow mass of sulphate was drained on porous glass and stirred with dilute ammonia (1200 c.c.); the deep maroon insoluble 2-nitro-7-aminoacridone was collected, washed and dried (17·5 g.; decomp. at 370—375° without melting). A sample was dissolved in boiling 95% pyridine and an excess of boiling water added to the filtered solution; after some time the *2-nitro-7-aminoacridone* separated in lustrous maroon prisms (decomp. 380°) (Found: C, 60·8; H, 3·7; N, 16·1. $C_{13}H_9O_3N_3$ requires C, 61·2; H, 3·5; N, 16·5%).

The foregoing crude compound (7 g.) was added to a solution of stannous chloride crystals (42 g.) in hydrochloric acid (42 c.c.) and the mixture heated on the water-bath for 1 hour when an almost clear solution was obtained. After some hours at 0°, the precipitate of the stannichloride complex was collected and stirred with cold 5N-sodium hydroxide (200 c.c.) for 1 hour. The insoluble material was separated, dissolved in dilute hydrochloric acid, traces of tin salts removed with hydrogen sulphide and the warm filtered solution (charcoal) basified with ammonia, 2:7-diaminoacridone being obtained as a pale yellow powder (5·7 g.); this was recrystallised from dilute pyridine to give the compound in glittering ochre tablets, m. p. 354—356° (Found: C, 69·1; H, 4·8; N, 18·8. Calc. for $C_{13}H_{11}ON_3$: C, 69·4; H, 4·9; N, 18·7%).

*5-Nitro-4′-dimethylaminophenylamine-2-carboxylic acid.* Potassium 2-chloro-4-nitrobenzoate (60 g.; 0·25 mol.), potassium carbonate (20 g.) and copper powder (1 g.) were stirred with amyl alcohol (400 c.c.) at 120°; freshly redistilled *p*-aminodimethylaniline (43 g.; 0·32 mol.) was added slowly over 20 minutes and the rapidly stirred mixture maintained at 120° ± 2° for 3 hours. The crude acid was isolated in the usual manner (vol. filtrate 400 c.c.), washed, dissolved in boiling water (225 c.c.) containing potassium carbonate (20 g.) and a solution of potassium chloride (15 g.) in boiling water (50 c.c.) added; the potassium salt separated after some hours at 0° in glistening black prisms. It was dissolved in boiling water (600 c.c.) and the acid precipitated at pH 4·0 with 5N-hydrochloric acid, *5-nitro-4′-dimethylamino-diphenylamine-2-carboxylic acid* being obtained (37 g.; m. p. 216—218°); a sample crystallised from dilute dioxan in small glistening black tablets, m. p. 226—228° (decomp.) (Found: C, 60·3; H, 5·1; N, 14·1, 14·2. $C_{15}H_{15}O_4N_3$ requires C, 59·8; H, 4·9; N, 14·0%). The acid (5 g.) dissolved completely in 0·5N-hydrochloric acid (100 c.c.) at the boiling point but suffered some decomposition.

In two runs in which the *p*-aminodimethylaniline was added all at once to the other reactants at 140° the reaction became very violent; the stirring was continued for 5 hours at 140° (internal) and the product precipitated at pH 3 in the cold. The crude product (40 g.) was crystallised twice from dilute acetic acid and gave *p*-nitrobenzoic acid (23 g.) in the form of glittering yellow needles, m. p. 240—242° alone and in admixture with an authentic specimen (Found: *M*, by titration, 165. Calc.: *M*, 166).

*5-Chloro-2-nitro-7-dimethylaminoacridine.* 5-Nitro-4′-dimethylamino-diphenylamine-2-carboxylic acid (30 g.) was refluxed with phosphorus oxychloride (320 c.c.) for 4 hours. The cooled mixture was poured on to an excess of powdered ice and then ammonia slowly added with rapid stirring until the liquor was just alkaline, the temperature of the mixture being kept below 2°. The *5-chloro-2-nitro-7-dimethylaminoacridine* (29 g.; m. p. 254—260°) was collected, well washed with water, drained, and dried under reduced pressure. A sample crystallised from aqueous alcoholic pyridine as a purple black powder, m. p. 278—282°, but was still impure (Found: N, 14·2; Cl, 9·3. $C_{15}H_{10}O_2N_3Cl$ requires N, 13·95; Cl, 11·8).

*2-Nitro-7-dimethylaminoacridone.* Crude 5-chloro-2-nitro-7-dimethylaminoacridine (28 g.) was heated to 100° with 3·3N-hydrochloric acid (2 l.) for 12 hours and the relatively insoluble dark ochre crystalline deposit of *2-nitro-7-dimethylaminoacridone hydrochloride* separated from the hot solution (Found, after drying at 100°/2 mm.: N, 12·9; Cl, 10·3. $C_{15}H_{12}O_3N_3$,HCl requires N, 13·1; Cl, 11·1%). The filtrate was made alkaline with ammonia and the precipitated acridone collected and washed. This was combined with the hydrochloride and refluxed for 1½ hours with 8% sodium carbonate (2 l.), collected, washed and dried. The crude *2-nitro-7-dimethylaminoacridone* (24 g.), was obtained as a dark brown powder, m. p. 344—346° (Found: N, 14·95. $C_{15}H_{12}O_3N_3$ requires N, 14·8%); it was too insoluble in organic solvents for recrystallisation.

*2-Amino-7-dimethylaminoacridone.*—2-Nitro-7-dimethylaminoacridone (20 g.) was added in small portions to a solution of stannous chloride crystals (120 g.) in hydrochloric acid (120 c.c.). The mixture was heated on the water-bath for 1½ hours, the clear dark solution cooled and slowly added to stirred cold 5N-sodium hydroxide (800 c.c.), the temperature being maintained at < 40°. The *2-amino-7-dimethylaminoacridone* was collected, washed, dissolved in boiling water (200 c.c.) and hydrochloric acid (50 c.c.) and the filtered solution run into stirred cold 2·5N-sodium hydroxide (800 c.c.); after separation and washing, the compound was obtained as an olive-yellow powder (16·8 g.; m. p. 310—314°). A sample crystallised from aqueous alcoholic pyridine in yellow-brown needles, m. p. 312—314° (Found: C, 70·9; H, 6·0; N, 16·9. $C_{15}H_{15}ON_3$ requires C, 71·1; H, 5·9; N, 16·6%).

*2-Amino-7-dimethylaminoacridine.*—A solution of 2-amino-7-dimethylaminoacridone (4 g.) in warm N-hydrochloric acid (75 c.c.) was added dropwise to stirred cold 0·5N-sodium hydroxide (400 c.c.). The fine yellow suspension was saturated with carbon dioxide, heated to 80° and 4% sodium amalgam (220 g.) added in 7 portions over 1½ hours, the carbon dioxide stream and stirring being continuous during this period and for a further 1 hour at 80°. Ferric chloride solution (5%; 5 c.c.) was added and a current of oxygen passed in with rapid stirring for 1 hour at 60°. The dark chocolate-brown microcrystalline powder (3·2 g.; m. p. 234—242°) was separated, dissolved in boiling water (110 c.c.) and N-hydrochloric acid (18 c.c.) and the crimson purple solution filtered and rapidly heated to 80°. A hot solution (150 c.c.; 80° C.) of ammonium chloride–sodium chloride (saturated at 15° with 2 parts ammonium chloride and 1 part sodium chloride) was added; after scratching and cooling, the 2-amino-7-dimethylaminoacridine hydrochloride (3 g.) separated in glittering black prisms. The free diamine was obtained as a dark brick-red powder (2·2 g.) from the aqueous solution by precipitation with cold dilute sodium hydroxide. When this (1 g.) was dissolved in pyridine (25 c.c.), alcohol (10 c.c.) and water (10 c.c.), the solution filtered and heated to the b. p. and boiling water (200 c.c.) added, the solution, after 2 days at 0°, gave *2-amino-7-dimethylaminoacridine* (0·68 g.) in black rhombs with a metallic lustre. When these were dried at 110°/2 mm. they gave a brick-red powder, m. p. 254—256° (Found: C, 75·6, 75·4; H, 6·3, 6·3; N, 17·9, 17·8. $C_{15}H_{15}N_3$ requires C, 75·8; H, 6·3; N, 17·7%). The monohydrochloride was soluble to the extent of *ca.* 3% in water at 20° giving a purple crimson solution.

*5-Nitro-3'-aminodiphenylamine-2-carboxylic acid.* 2-Chloro-4-nitrobenzoic acid (10 g.), *m*-phenylenediamine (7 g.), potassium carbonate (7·5 g.), copper powder (0·2 g.) and amyl alcohol were stirred together at 150° (bath temperature) for 1½ hours. The crude product (9·5 g.), m. p. > 300°, was reprecipitated at the boiling point from the 10% solution in dilute ammonia, but was still impure *5-nitro-3'-aminodiphenylamine-2-carboxylic acid* (Found: N, 15·2; *M*, by titration, 252. $C_{13}H_{11}O_4N_3$ requires N, 15·4%; *M*, 273). It was acetylated with acetic anhydride in 10% solution in cold aqueous sodium carbonate; the *5-nitro-3'-acetamido-diphenylamine-2-carboxylic acid* crystallised from aqueous alcohol in scarlet needles, m. p. 242—244° (Found: N, 13·2. $C_{15}H_{13}O_5N_3$ requires N, 13·3%).

*2-Nitro-8-aminoacridone and 2 : 8-Diaminoacridone.*—The foregoing crude nitroaminodiphenylamine-2-carboxylic acid (4·3 g.) was heated with sulphuric acid (30 c.c.) at 100° for 1½ hours, poured on ice (200 g.) and the yellow precipitate collected. This was ground with aqueous ammonia, collected and washed, *2-nitro-8-aminoacridone* being obtained as a yellow-brown powder (3·5 g.). It was recrystallised from aqueous pyridine and obtained in brown needles, m. p. > 400° (Found: N, 16·7. $C_{13}H_9O_3N_3$ requires N, 16·5%).

The crude material (3 g.) was heated on the water bath with stannous chloride crystals (30 g.) and hydrochloric acid (30 c.c.) for 2 hours. After cooling, the precipitate was separated, stirred with excess of cold 5N-sodium hydroxide and the insoluble material collected, washed with water and dried, 2 : 8-diaminoacridone being obtained as a yellow powder (2·0 g.); recrystallisation from aqueous pyridine gave the compound in felted yellow needles, m. p. 368—370°. Reduction with sodium amalgam gave 2 : 8-diaminoacridine which crystallised from aqueous pyridine in yellow needles, m. p. 284—286° alone and in admixture with authentic material.

*3' : 5-Dinitrodiphenylamine-2-carboxylic acid.* 2-Chloro-4-nitrobenzoic acid (10 g.), *m*-nitroaniline (7 g.), potassium carbonate (7·5 g.), amyl alcohol (40 c.c.) and copper powder (0·2 g.) were stirred at 150° (bath temperature) for 2 hours. The crude product (3·5 g.) was crystallised twice from aqueous alcohol and gave 3' : 5-dinitrodiphenylamine-2-carboxylic acid in orange brown needles (2 g.), m. p. 262° (cf. Albert and Linnell, *loc. cit.*). Cyclisation of the crude acid (1·6 g.) with sulphuric acid (16 c.c.) at 100° for 1 hour gave 2 : 6-dinitroacridone which on reduction with stannous chloride and hydrochloric acid as described above yielded 2 : 6-diaminoacridone (1·1 g.); it crystallised from aqueous pyridine in yellow needles, m. p. 300—302°. When mixed with 2 : 8-diaminoacridone (m. p. 368—370°) prepared by cyclisation of 5-nitro-3'-aminodiphenylamine-2-carboxylic acid followed by reduction the m. p. was 300° with softening and sintering at 290°.

*5 : 4'-Di(acetamido)diphenylamine-2-carboxylic acid.*—2-Chloro-4-acetamidobenzoic acid (10 g.), *p*-aminoacetanilide, potassium carbonate (7·5 g.), copper powder (0·2 g.) and amyl alcohol (40 c.c.) were stirred at 145—150° (bath temperature) for 1 hour. The crude product (11 g.) was recrystallised from aqueous alcohol and gave *5 : 4'-di(acetamido)diphenylamine-2-carboxylic acid* (8 g.) in brown needles, m. p. 244—246° alone and in admixture with a sample prepared as described above. Cyclisation of the crude acid (11 g.) in the manner previously described for 4'-amino-5-acetamidodiphenylamine-2-carboxylic acid yielded 2 : 7-diaminoacridone (6 g.) which, on recrystallisation from aqueous pyridine, was obtained in brown leaves, m. p. 356—358°.

*Series Derived from 5-Substituted 2-Chlorobenzoic Acid.*

*2-Chloro-5-nitrobenzoic Acid* (cf. Hubner, *Annalen*, 1883, **222**, 195; Lehmstedt, *Ber.*, 1931, **64**, 2381).—*o*-Chlorobenzoic acid (100 g.) was dissolved in sulphuric acid (300 c.c.) and a solution of nitric acid (32 c.c.; *d*, 1·50) in sulphuric acid (68 c.c.) added with stirring at such a speed that the reaction temperature maintained itself at 50—55°. After some hours the mixture was added to an excess of ice and the precipitate collected, washed and dissolved in boiling water (3 l.). The solution was allowed to cool to 40° and the crystals of 2-chloro-5-nitrobenzoic acid (91 g.; m. p. 164—165°) collected and washed with water. The filtrate contained appreciable amounts of 2-chloro-5-nitro- and 2-chloro-3-nitro-benzoic acid which separated on freezing.

*2-Chloro-5-acetamidobenzoic acid.* The foregoing acid (100 g.), water (1 l.), hydrochloric acid (3 c.c.), and iron powder (100 g., " Pacteron No. 2 ") were stirred at 90—95° for 6 hours. The mixture was made just alkaline to phenolphthalein with 5N-sodium hydroxide and filtered whilst hot; adjustment to pH *ca.* 3 of the cooled filtrate precipitated 2-chloro-5-aminobenzoic acid (74 g.), m. p. 187—188° (Found: *M*, by titration, 169. Calc.: *M*, 171·5). The acid (20 g.) was dissolved in water (200 c.c.) and sodium carbonate (20 g.) and acetic anhydride (14 c.c.) added with stirring at such a speed that the temperature did not exceed 25°; after stirring for a further ½ hour more acetic anhydride (4 c.c.) was added and the stirring continued for another ½ hour. Acidification to pH *ca.* 3 precipitated 2-chloro-5-acetamidobenzoic acid (24·6 g.; m. p. 215°). A sample crystallised from water in colourless prisms, m. p. 216° (Found: *M*, by titration, 213. Calc.: *M*, 213·5).

*4-Nitro-3'-aminodiphenylamine-2-carboxylic acid.* 2-Chloro-5-nitrobenzoic acid (10 g.), *m*-phenylenediamine (7 g.), potassium carbonate (7·5 g.), copper powder (0·2 g.) and amyl alcohol (40 c.c.) were stirred at 150° (bath temperature) for 1½ hours. The crude product when purified by reprecipitation from its hot solution in dilute ammonia yielded *4-nitro-3'-aminodiphenylamine-2-carboxylic acid* (7·8 g.), m. p. 300° (Found: N, 15·6; *M*, by titration, 265. $C_{13}H_{11}O_4N_3$ requires N, 15·4%; *M*, 273). The compound was difficult to purify and was characterised by acetylation in dilute sodium carbonate solution with acetic anhydride, *4-nitro-3'-acetamidodiphenylamine-2-carboxylic acid* being obtained which crystallised from aqueous alcohol in yellow needles, m. p. 292—294° (Found: N, 13·3; *M*, by titration, 318. $C_{15}H_{13}O_5N_3$ requires N, 13·3%; *M*, 315).

*7-Nitro-2-aminoacridone and 2 : 7-diaminoacridone.* The foregoing crude nitroaminodiphenylamine-2-carboxylic acid (3·7 g.) was heated with sulphuric acid (25 c.c.) at 100° for 1½ hours and poured on to ice. The insoluble material was separated, stirred with excess of dilute ammonia and collected; it could not be satisfactorily purified owing to its insolubility and was accordingly directly reduced. The material was added to a solution of stannous chloride crystals (20 g.) in hydrochloric acid (20 c.c.), the mixture heated on the water-bath for 1 hour, diluted with hot water and filtered (charcoal). Basification with 5N-sodium hydroxide precipitated 2 : 7-diaminoacridone which after dissolution in dilute hydrochloric acid, filtering with charcoal and reprecipitating amounted to 1 g. Recrystallisation from aqueous pyridine gave 2 : 7-diaminoacridone in greenish-brown leaves, m. p. 352—354° alone and in admixture with that obtained from the cyclisation and reduction of 5-nitro-4'-aminodiphenylamine-2-carboxylic acid of which the constitution follows from the method of synthesis (Found: N, 18·6. Calc.: N, 18·7%).

*4 : 3'-Dinitrodiphenylamine-2-carboxylic acid.* 2-Chloro-5-nitrobenzoic acid (10 g.), *m*-nitroaniline (7 g.), potassium carbonate (7·5 g.), copper powder (0·2 g.) and amyl alcohol (40 c.c.) were stirred at 155° (bath temperature) for 5 hours. The crude product, isolated in the normal manner, was recrystallised from aqueous alcohol and gave 4 : 3'-dinitrodiphenylamine-2-carboxylic acid (1·3 g.) in brown needles, m. p. 288—290° (Albert and Linnell, J., 1938, 22, record m. p. 220°) (Found: N, 13·9; *M*, by titration, 299. Calc. for $C_{13}H_9O_6N_3$: N, 13·9%; *M*, 303).

*3 : 6-Diaminoacridone.*—The foregoing acid (1·1 g.) and sulphuric acid (11 c.c.) were heated at 100° for 1 hour and the resulting dinitroacridone isolated in the usual manner. The crude product was heated on the water bath with a solution of stannous chloride crystals (10 g.) in hydrochloric acid (10 c.c.) for 1 hour, diluted with boiling water, filtered hot (charcoal), strongly basified with cold 5N-sodium hydroxide and the precipitate collected and washed. Recrystallisation

of this (0·6 g.) gave 3 : 6-diaminoacridone in brown needles, m. p. 314—316°; this m. p. was depressed when the substance was mixed with 2 : 7-diaminoacridone (m. p. 354°) obtained by cyclisation of 4-nitro-3′-aminodiphenylamine-2-carboxylic acid.

4 : 4′-*Dinitrodiphenylamine-2-carboxylic Acid and* 3 : 7-*Diaminoacridone*.—The acid was obtained by the method of Bogert and Hirschfielder (*loc. cit.*) and the crude material purified through the insoluble ammonium salt. It had m. p. 292° (lit. 293°) (Found: N, 14·1; *M*, by titration, 303. Calc. for $C_{13}H_9O_6N_3$: N, 13·9%; *M*, 303).

Cyclisation with sulphuric acid followed by reduction with stannous chloride–hydrochloric acid gave 3 : 7-diaminoacridone which crystallised in golden yellow needles from aqueous pyridine, m. p. 320° (Bogert and Hirschfielder give m. p. 325°).

3′-*Amino*-4-*acetamidodiphenylamine-2-carboxylic acid*. 2-Chloro-5-acetamidobenzoic acid (10 g.), *m*-phenylenediamine (8 g.), potassium carbonate (7 g.), copper powder (0·2 g.) and amyl alcohol (40 c.c.) were heated at 150° (bath temperature) for 1½ hours. The product isolated in the normal manner by precipitation was obtained in yellow-green needles (10 g.), m. p. 152—154° (Found: N, 14·3; *M*, by titration, 285. $C_{15}H_{15}O_3N_3$ requires N, 14·7%; *M*, 285. Acetylation with acetic anhydride in cold dilute sodium carbonate solution gave 4 : 3′-*di*(*acetamido*)*diphenylamine*-2-*carboxylic acid* in yellow-green needles, m. p. 264—265° (Goldstein *et al.*, *Helv. Chim. Acta*, 1927, **10**, 603, give m. p. 252°) (Found: N, 12·8; *M*, by titration, 315. $C_{17}H_{17}O_4N_3$ requires N, 12·9%; *M*, 327).

2 : 7-*Diaminoacridone and* 2 : 7-*Diaminoacridine*.—The foregoing 3′-amino-4-acetamidodiphenylamine-2-carboxylic acid (6 g.) was heated with sulphuric acid (42 c.c.) at 100° for 1½ hours, water (20 c.c.) added and the heating continued for a further ½ hour. The reaction mixture was cooled, poured into an excess of ammonia and the crude 2 : 7-diaminoacridone collected and washed (4·0 g.). This was purified by reprecipitation from its solution in dilute hydrochloric acid and then recrystallised from dilute pyridine, 2 : 7-diaminoacridone being obtained in clusters of green-brown needles, m. p. 354—356° (Found: N, 18·8. Calc.: N, 18·7%). Reduction with sodium amalgam followed by oxygenation in the same manner as described for the 3 : 6-isomeride gave 2 : 7-diaminoacridine (60%) which on crystallisation from dilute pyridine was obtained in orange-brown plates, m. p. 352—354° (Found: N, 20·4. Calc.: N, 20·1%).

3′-*Nitro*-4-*acetamidodiphenylamine-2-carboxylic acid*. 2-Chloro-5-acetamidobenzoic acid (11 g.), *m*-nitroaniline (8·6 g.), potassium carbonate (7·2 g.), copper powder (0·2 g.) and amyl alcohol (40 c.c.) were stirred at 150° (bath temperature) for 2 hours. The crude acid isolated was extracted with boiling water (3 × 300 c.c.) and the insoluble material recrystallised from dilute alcohol, 3′-*nitro*-4-*acetamidodiphenylamine-2-carboxylic acid* being obtained in clusters of orange needles (5 g.), m. p. 250° (Found: N, 13·4; *M*, by titration, 310. $C_{15}H_{13}O_5N_3$ requires N, 13·3%; *M*, 315).

6-*Nitro*-3-*amino- and* 3 : 6-*Diamino-acridone*.—The above acid (3·3 g.) was heated with sulphuric acid (23 c.c.) at 100° for 2 hours, water (10 c.c.) added and the heating continued for a further ½ hour. Water (100 c.c.) was added, the resulting solution basified with ammonia and the precipitated 6-*nitro*-3-*aminoacridone* (2·5 g.) collected; recrystallisation from dilute pyridine gave the compound in brown needles which, on drying at 100°, fell to a brick-red powder, m. p. 340—342° (Found: C, 61·0; H, 3·9; N, 16·5. $C_{13}H_9O_3N_3$ requires C, 61·2; H, 3·5; N, 16·5%).

The crude nitroaminoacridone (1·0 g.) was heated to 100° for 1 hour with hydrochloric acid (7 c.c.) and stannous chloride crystals (7 g.). After cooling, the insoluble stannichloride complex was collected, stirred with excess of cold 5N-sodium hydroxide and the 3 : 6-diaminoacridone separated and washed with water (0·8 g.). Recrystallisation from aqueous pyridine gave the pure compound in brown needles, m. p. 312—314° (Found: C, 69·1; H, 5·0; N, 18·8. Calc. for $C_{13}H_{11}ON_3$: C, 69·4; H, 4·9; N, 18·7%).

3 : 6-*Diaminoacridine*. The above 3 : 6-diaminoacridone (2 g.) was suspended in 60% ethyl alcohol (125 c.c.), 4% sodium amalgam (80 g.) added and the mixture stirred at room temperature for 6 hours during which time the suspension was kept saturated with carbon dioxide. The mixture was then heated to 60° and, whilst rapidly stirred, a current of air passed in for 2 hours at this temperature. After cooling, the insoluble material was collected, dissolved in dilute hydrochloric acid, the solution filtered (charcoal) and basified with ammonia. The precipitate was collected (1·5 g.) and recrystallised from dilute pyridine, 3 : 6-diaminoacridine being obtained in chocolate prisms, m. p. 254—256° (Found: C, 74·0; H, 5·3; N, 20·0. Calc. for $C_{13}H_{11}N_3$: C, 74·6; H, 5·3; N, 20·1%). Albert and Linnell, *loc. cit.*, record m. p. 322°.

### *Monosubstituted Diphenylamine-2-carboxylic Acids.*

3-*Nitrodiphenylamine-2-carboxylic Acid*.—2-Chloro-6-nitrobenzoic acid (10 g.), aniline (20 c.c.), potassium carbonate (7 g.) and copper powder (0·5 g.) were stirred at 180° (bath temperature) for 1 hour. The crude acid (3·5 g.), recrystallised from aqueous methanol, gave the pure compound in yellow-brown prisms, m. p. 174° (Lehmstedt and Schrader, *Ber.*, 1937, **70**, 1526, give m. p. 172°) (Found: *M*, by titration, 259. Calc. for $C_{13}H_{10}O_4N_2$: *M*, 258). Repeated attempts to obtain 4-nitroacridone from this by cyclisation with sulphuric acid were unsuccessful.

3-*Acetamidodiphenylamine-2-carboxylic Acid*.—2-Chloro-6-acetamidobenzoic acid (10 g.), aniline (7·6 c.c.), potassium carbonate (7 g.), copper powder (0·2 g.) and amyl alcohol (40 c.c.) were stirred at 145—150° (bath temperature) for 2 hours. The crude product was recrystallised from aqueous alcohol and gave 3-*acetamidodiphenylamine-2-carboxylic acid* (4 g.) in yellow needles, m. p. 160° (Found: N, 10·5; *M*, by titration, 273. $C_{15}H_{14}O_3N_2$ requires N, 10·4%; *M*, 270).

4-*Aminoacridone*.—Cyclisation of the above acid with concentrated sulphuric acid failed to yield 4-aminoacridone. The acid (2 g.) was heated with 75% sulphuric acid (20 c.c.) at 100° for 2 hours, water (6 c.c.) added and the heating continued for a further ½ hour. The crude material was a dark solid gum, insoluble in alkali; this was extracted with methanol, and from the solution, after some hours, the crystalline deposit was collected. Recrystallisation from the same solvent gave 4-aminoacridone (0·05 g.) in pale yellow needles, m. p. 290—292° alone and in admixture with that obtained by the cyclisation of 3′-nitrodiphenylamine-2-carboxylic acid followed by reduction (Found: N, 13·3. Calc. for $C_{13}H_{10}ON_2$: N, 13·3%).

4-*Acetamidodiphenylamine-2-carboxylic acid*. 2-Chloro-5-acetamidobenzoic acid (10 g.), aniline (7·6 g.), potassium carbonate (7 g.), copper powder (0·2 g.) and amyl alcohol (40 c.c.) were stirred at 150° (bath temperature) for 1½ hours. The crude product on recrystallisation from 50% alcohol (100 c.c.) gave 4-*acetamidodiphenylamine-2-carboxylic acid* as a mass of felted yellow needles (7·1 g.), m. p. 236—238° (Found: N, 10·6; *M*, by titration, 270. $C_{15}H_{14}O_3N_2$ requires N, 10·4%; *M*, 270).

3-*Aminoacridone*-7(?)-*sulphonic acid*. The foregoing acid (1·5 g.) was heated with sulphuric acid (15 c.c.) for 4 hours at 100°, water (5 c.c.) added and the heating continued for a further ½ hour. The solution was cooled, diluted with water (50 c.c.) and, after chilling, the precipitate collected; this was redissolved in dilute ammonia and reprecipitated at the boiling point by acidification to pH 2·0—2·5 with hydrochloric acid. The yellow microcrystalline precipitate which slowly separated was collected and dried (1·4 g.); analysis showed it to be an *aminoacridone sulphonic acid* probably the 3 : 7-isomeride (Found: N, 9·6; *M*, by titration, 298. $C_{13}H_{10}O_4N_2S$ requires N, 9·7%; *M*, 290).

It was not found possible to effect *cyclo*dehydration of 4-acetamidodiphenylamine-2-carboxylic acid with production of 3-aminoacridone; with 80% sulphuric acid, or with 100% sulphuric acid for a shorter time, the only alkali insoluble material obtained was 4-aminodiphenylamine-2-carboxylic acid.

4-*Nitrodiphenylamine-2-carboxylic acid*. 2-Chloro-5-nitrobenzoic acid (10 g.), potassium carbonate (7 g.), aniline

(20 c.c.) and copper powder (0·2 g.) were stirred at 180° (bath temperature) for 1½ hours. After removal of the aniline in steam, potassium chloride (10 g.) was dissolved in the boiling filtered solution (vol. 250 c.c.) which was then allowed to stand on ice. The scarlet needles of the potassium salt were collected, dissolved in boiling water and the solution acidified with dilute hydrochloric acid, 4-nitrodiphenylamine-2-carboxylic acid separating as a yellow-green crystalline mass (9·7 g.), m. p. 256—258° (Found: N, 11·1; *M*, by titration, 250. $C_{13}H_{10}O_4N_2$ requires N, 10·9%; *M*, 258). Attempted cyclisation of this compound with concentrated and with 70% and 90% sulphuric acid failed to yield 3-nitroacridone.

6-*Nitrodiphenylamine-2-carboxylic acid.* 2-Chloro-3-nitrobenzoic acid (10 g.), aniline (20 c.c.), potassium carbonate (7·5 g.) and copper powder (0·2 g.) were stirred at 160° (bath temperature) for 1 hour. After removal of the excess aniline in steam, the product was isolated in the usual manner in the form of an orange-yellow crystalline mass (11 g.). This, on recrystallisation from dilute alcohol, gave the pure compound in orange prisms, m. p. 195—196° (Found: N, 11·0. Calc. for $C_{13}H_{10}O_4N_2$: N, 10·9%) (cf. Tuttle, *loc. cit.*).

1-*Nitroacridone.*—The foregoing acid (2 g.) was heated with sulphuric acid (14 c.c.) for 1 hour at 100°, poured on to ice (60 g.) and, after standing, the yellow precipitate collected, washed with warm dilute ammonia and dried. The crude 1-nitroacridone (1·25 g.) crystallised from dilute pyridine in orange needles, m. p. 260—262° alone and in admixture with that obtained by the cyclisation of 2′-nitrodiphenylamine-2-carboxylic acid (Ullmann, *loc. cit.*) (Found: N, 11·8. Calc.: N, 11·7%).

*Attempted Condensation of* 2-*Chloro*-3-*acetamidobenzoic Acid with* m-*Phenylenediamine.*—2-Chloro-3-acetamidobenzoic acid (5 g.), *m*-phenylenediamine (4 g.), potassium carbonate (3·25 g.), copper powder (0·2 g.) and amyl alcohol (20 c.c.) were stirred at 150° (bath temperature) for 1½ hours. Isolation of the product in the usual manner yielded *m*-acetamidobenzoic acid (3·6 g.); it was recrystallised from aqueous alcohol (charcoal) and pure *m*-acetamidobenzoic acid obtained in colourless needles, m. p. 252° alone and in admixture with authentic material (Found: N, 8·1; *M*, by titration, 180. Calc.: N, 7·8%; *M*, 179).

Lowering the reaction temperature to 100° failed to effect the desired Ullmann condensation; dehalogenation took place with production of *m*-acetamidobenzoic acid in *ca.* 85% yield.

With *m*-nitroaniline and 2-chloro-5-acetamidobenzoic acid no reaction took place at temperatures in the region of 120°; at 150° (bath temperature) dehalogenation with production of *m*-acetamidobenzoic acid took place.

5-*Acetamidodiphenylamine-2-carboxylic acid.* 2-Chloro-4-acetamidobenzoic acid (10 g.), potassium carbonate (7·5 g.), copper powder (0·2 g.) and aniline (20 c.c.) were stirred at 180° (bath temperature) for 90 minutes. After removal of the aniline by distillation in steam, the crude product was isolated and recrystallised from aqueous alcohol giving 5-*acetamidodiphenylamine-2-carboxylic acid* (5 g.) as a mass of buff needles, m. p. 248—250° (Found: N, 10·5; *M*, by titration, 267. $C_{15}H_{14}O_3N_2$ requires N, 10·4%; *M*, 270).

2-*Aminoacridone-7-sulphonic acid.* A solution of the foregoing acid (1·5 g.) in sulphuric acid (15 c.c.) was heated at 100° for 1 hour; water (4 c.c.) was added, the mixture heated at 100° for a further 30 minutes to effect deacetylation, poured on to ice (50 g.) and the precipitate collected. This dissolved completely in dilute ammonia; the solution was filtered (charcoal) and adjusted to pH *ca.* 2 at the boiling point with hydrochloric acid. A microcrystalline precipitate of the aminoacridone sulphonic acid gradually separated (0·5 g.), m. p. > 400°, which would appear to be the 2 : 7-isomeride (Found: N, 9·7; *M*, by titration, 305. Calc. for $C_{13}H_{10}O_4N_2S$: N, 9·7%; *M*, 290).

5-*Nitrodiphenylamine-2-carboxylic acid* (cf. Ullmann, *loc. cit.*). 2-Chloro-4-nitrobenzoic acid (50 g.), potassium carbonate (50 g.), copper powder (1 g.), amyl alcohol (150 c.c.) and aniline (200 c.c.) were stirred at 140° for 4½ hours. After removal of the amyl alcohol and excess aniline in a current of steam, the filtered (charcoal) solution was evaporated to small volume and allowed to stand at 0°; the crystalline mass was drained (vol. filtrate, 180 c.c.), dissolved in boiling water (500 c.c.) and adjusted to pH 2 with hydrochloric acid. The yellow microcrystalline precipitate of 5-nitrodiphenylamine-2-carboxylic acid was collected and dried (yield 50—52 g.); this was sufficiently pure for further use. It crystallised from 95% alcohol in long yellow needles, m. p. 232—234°.

2-*Nitroacridone* (cf. Ullmann, *loc. cit.*; Albert and Linnell, *loc. cit.*). Anhydrous 5-nitrodiphenylamine-2-carboxylic acid (50 g.) was gently refluxed with phosphorus oxychloride (500 c.c.) for 4 hours. A portion (*ca.* one-third) of the oxychloride was removed by distillation under reduced pressure and the residue, while still hot, slowly mixed with powdered ice (2 kg.). Ammonia was added with rapid stirring until the solution was just alkaline (pH 9), the temperature being maintained below 3°. The precipitate was collected, washed and dried at 20° over potassium hydroxide, 5-chloro-2-nitroacridine (50 g.) being obtained as an olive-green powder; a sample crystallised from a large volume of benzene in long olive needles, m. p. 208° (Found: Cl, 13·6. Calc.: Cl, 13·7%). No tendency towards replacement of the nitro group by chlorine was observed under these experimental conditions; contrast Albert and Linnell (*loc. cit.*) who used less phosphorus oxychloride and, consequently, a higher temperature. The crude 5-chloro-2-nitroacridine was boiled with 3·3N-hydrochloric acid (1500 c.c.) for 3 hours, the insoluble nitroacridone collected, washed and extracted with boiling 2½% sodium carbonate solution for ½ hour. The insoluble yellow 2-nitroacridone was collected, washed and dried (44 g., m. p. > 400°).

2 : 7-*Dinitroacridone.*—Anhydrous 2-nitroacridone (72 g.; 0·3 mol.) was dissolved in sulphuric acid (300 c.c.; *d*, 1·82—1·84) by stirring at 25°. A solution of nitric acid (14·5 c.c.; 0·345 mol.; *d*, 1·5) in sulphuric acid (100 c.c.) was then added dropwise with rapid stirring over 15 minutes, the temperature being maintained at 25—30° during the addition. Stirring was maintained at this temperature for a further 2 hours, the temperature raised to 70° over ¼ hour and maintained at 70—75° with stirring for a further ½ hour. The solution was poured on to crushed ice (2 kg.), the yellow precipitate collected, washed and extracted by boiling with 8% sodium carbonate solution (2 l.) for ½ hour to remove any trinitroacridone which is soluble in sodium carbonate. The insoluble material was collected, washed and dried, 2 : 7-dinitroacridone being obtained as a fine yellow powder (73 g.), m. p. 360—366°. A sample was dissolved in boiling 95% pyridine and a large excess of boiling water added to the filtered solution; the 2 : 7-dinitroacridone slowly crystallised in almost quantitative amount in long golden-brown needles (Found: C, 55·0; H, 2·7; N, 15·0. Calc. for $C_{13}H_7O_5N_3$: C, 54·8; H, 2·5; N, 14·7%).

2 : 7-*Diaminoacridone.*—The foregoing crude dinitroacridone (76 g.) was added in small portions to a hot stirred solution of stannous chloride crystals (780 g.) in 10N-hydrochloric acid (780 c.c.) at such a rate that the internal temperature was maintained at 85—90°; the addition took *ca.* 30 minutes and at the end of this time an almost clear solution was obtained. The solution was stirred for a further 45 minutes at 90° and then allowed to stand at 0°; after some hours, the pasty mass was drained at the pump. The solid was added in portions to stirred cold 5N-sodium hydroxide (2 l.) and, after stirring for a further 1 hour, the insoluble yellow material was collected, dissolved in hot 2N-hydrochloric acid (1 l.) and residual traces of tin removed with hydrogen sulphide. The filtered solution was cooled, nearly neutralised with cold 5N-sodium hydroxide and then basified with excess of 2½% sodium carbonate solution with stirring. The insoluble material was collected, washed and dried at 20°, 2 : 7-diaminoacridone being obtained as a light yellow powder (58—60 g.; m. p. 348—352°). A sample crystallised from dilute pyridine in golden-brown leaves, m. p. 354—356° (Found: C, 69·1; H, 4·9; N, 18·8. Calc. for $C_{13}H_{11}ON_3$: C, 69·4; H, 4·9; N, 18·7%).

2 : 7-*Diaminoacridine.*—The above crude 2 : 7-diaminoacridone (20 g.) was dissolved in boiling N-hydrochloric acid

(375 c.c.) and the filtered solution run into rapidly stirred cold 0·5N-sodium hydroxide (1 l.) to precipitate the diaminoacridone as a fine bright olive-yellow powder. The suspension was saturated with carbon dioxide, heated to 80° and 4% sodium amalgam (1 kg.) added in 7 portions over a period of 1½ hours to the rapidly stirred suspension at 80—82°; stirring was continued at this temperature for a further 1½ hours, and the passage of carbon dioxide maintained throughout. Ferric chloride solution (5%, 20 c.c.) was added to the golden-yellow suspension and a fast stream of oxygen passed for 1½ hours with rapid stirring at 60—62°; the chocolate-brown suspension had then become crystalline. The 2 : 7-diaminoacridine (15·5 g.; m. p. 350—352°) was washed and dried at 25°. When crystallised from aqueous alcoholic pyridine, the pure compound was obtained in glittering golden leaves, m. p. 354—356° (shrinking at 350°) alone and in admixture with material obtained by cyclisation of 3'-amino-4-acetamidodiphenylamine-2-carboxylic acid followed by reduction (Found: C, 74·5; H, 5·0; N, 20·0. Calc. for $C_{13}H_{11}N_3$: C, 74·6; H, 5·3; N, 20·1%).

The crude diaminoacridine (15·5 g., 0·075 mol.), suspended in boiling water (425 c.c.), immediately gave a purple solution on addition of the theoretical amount of N-hydrochloric acid (75 c.c.). The filtered solution was heated quickly to 80° and the hot (80°) salting-out-solution (500 c.c.) added, followed by a further quantity (250 c.c.) when the solution had cooled to 60°. Crystallisation was facilitated by scratching and the mixture was set aside at 20° for several hours. 2 : 7-Diaminoacridine monohydrochloride was obtained as a mass of glistening black tablets having the appearance of grains of marcassite (16·5—17·0 g.). [The salting-out-solution was prepared by mixing 1 vol. of sodium chloride solution (saturated at 15°) with 2 vols. of ammonium chloride solution (saturated at 15°)]. The hydrochloride (1 g.) was dissolved in hot water (25 c.c.) and the red solution added to cold N-sodium hydroxide (50 c.c.) with stirring; the free diamine was precipitated as a pale yellow powder which, after collection, washing and drying at 10 mm., amounted to 0·8 g., m. p. 350—354° (Found: N, 20·1%). When recrystallised from dilute alcoholic pyridine the compound was obtained as glistening golden leaves, m. p. 354—356° (Found: N, 20·0, 20·2%). The monohydrochloride (1 g.) was dissolved in boiling 33% ethyl alcohol (40 c.c.) and 3N-alcoholic ammonia (6 c.c.) added to the boiling filtered red solution; after scratching whilst almost boiling for a few minutes, 2 : 7-diaminoacridine separated (0·67 g.) as a mass of glittering golden spangles, m. p. 354—356° (Found: N, 20·1%).

2- *and* 4-*Nitroacridones and* 2- *and* 4-*Aminoacridones.*—3'-Nitrodiphenylamine-2-carboxylic acid was prepared by the method described by Ullmann (*loc. cit.*) and by Lehmstedt and Schrader (*loc. cit.*). The acid (62 g.) was cyclised with sulphuric acid and the crude product (52 g.) separated into its components by fractional crystallisation from aqueous pyridine. From the less soluble fractions 2-nitroacridone (8·5 g.), m. p. >400°, was obtained and the more soluble fractions yielded 4-nitroacridone (35 g.), m. p. 362—364°. Reduction of these separately with stannous chloride followed by sodium amalgam gave 2-aminoacridone, m. p. 300—302°, and 2-aminoacridine, m. p. 222°, and also 4-aminoacridone, m. p. 292—294°, and 4-aminoacridine, m. p. 172—174° (Lehmstedt effected separation of the 2- and 4-nitroacridones through the corresponding 2- and 4-nitro-derivatives of 5-chloroacridine).

*Nitration of* 4-*Nitroacridone.*—3 : 6-*Dinitroacridone,* 3 : 6-*diaminoacridone and* 3 : 6-*diaminoacridine.* 4-Nitroacridone (39 g.) was nitrated in the same way as the 2-isomeride except that the addition of the nitrating mixture was made at 10° after which the solution was stirred for 2 hours at 20° and then ½ hour at 75°. A portion of the crude 3 : 6-dinitroacridone (44 g.) was recrystallised from aqueous pyridine and obtained in golden-brown plates, m. p. 388—390° (Found: N, 15·2. Calc.: N, 14·7%).

The crude 3 : 6-dinitroacridone (35 g.) was reduced with stannous chloride similarly to the 2 : 7-isomeride and gave 3 : 6-diaminoacridone as a yellow-brown powder (24 g.; m. p. 308—310°); this crystallised from aqueous pyridine in golden-brown needles, m. p. 314—316° alone and when mixed with the substance obtained by the cyclisation of 4 : 3'-dinitrodiphenylamine-2-carboxylic acid and subsequent reduction (Found: N, 18·8. Calc.: N, 18·7%).

Crude 3 : 6-diaminoacridone (4·7 g.) was dissolved in 60% ethanol (400 c.c.), 4% sodium amalgam (200 g.) added and carbon dioxide passed with stirring for 2 hours at room temperature and then for a further 1 hour at 60°. Ferric chloride solution (10%; 5 c.c.) was added and a current of air drawn through the rapidly stirred solution at 60° for 1½ hours. After the addition of alcohol (200 c.c.) the hot solution was filtered and most of the alcohol distilled away on the water bath; on adding ammonia (10 c.c., *d*, 0·880) 3 : 6-diaminoacridine separated in dark brown prisms (3·5 g.). Recrystallisation from aqueous alcohol gave the pure compound in brown prisms, m. p. 252—254° alone and in admixture with the diaminoacridine obtained by cyclisation of 3'-nitro-4-acetamidodiphenylamine-2-carboxylic acid and subsequent reduction (Found: N, 20·3. Calc.: N, 20·1%).

### 5-*Amino-* *and* 8-*Chloro-*5-*amino-*3-*dimethylaminoacridine.*

4'-*Dimethylaminodiphenylamine-*2-*carboxylic Acid* (cf. Drozdov, *J. Gen. Chem. Russ.*, 1939, **9**, 1373).—2-Chlorobenzoic acid (39 g.), potassium carbonate (40 g.), copper powder (1 g.), freshly distilled *p*-aminodimethylaniline (43 g.) and amyl alcohol (400 c.c.) were stirred at 140—145° (bath temperature) for 4 hours. The crude acid, isolated in the usual manner, was redissolved in boiling water (500 c.c.) containing a slight excess of potassium carbonate and reprecipitated at pH 4; the product (42 g.) was recrystallised from the minimum amount of alcohol (650 c.c.) and 4'-dimethylaminodiphenylamine-2-carboxylic acid (30 g.) obtained as a mass of olive-green needles, m. p. 224—226° (Found: *M*, by titration, 254. Calc.: *M*, 256).

5-*Chloro-*3-*dimethylaminoacridine.*—Anhydrous 4'-dimethylaminodiphenylamine-2-carboxylic acid (30 g.) was refluxed with phosphorus oxychloride (300 c.c.) for 4 hours and then *ca.* 100 c.c. of the oxychloride distilled off. The residue was mixed with excess of powdered ice and then ammonia and ice were added with rapid stirring until the liquor was alkaline to phenolphthalein, the temperature not being allowed to exceed 3°. The precipitated 5-chloro-3-dimethylaminoacridine was collected, drained on porous porcelain and dried under reduced pressure (30 g.); crystallisation from *cyclo*hexane (300 c.c.) gave the compound in long crimson needles, m. p. 158—160° (21 g.) (Found: N, 11·0; Cl, 13·6. Calc. for $C_{15}H_{13}N_3Cl$: N, 10·9; Cl, 13·8%).

5-*Amino-*3-*dimethylaminoacridine.* A solution of 5-chloro-3-dimethylaminoacridine (10 g.) in phenol (80 g.) was heated at 110° for 1 hour and then powdered ammonium carbonate (8 g.) added over 15 minutes with stirring; the solution was heated at 105° for a further 2 hours, cooled and poured into an excess of ether. The red precipitate was collected, refluxed for 1½ hours with methanol (800 c.c.) and the filtered solution evaporated to smaller volume (*ca.* 400 c.c.); on cooling, 5-*amino-*3-*dimethylaminoacridine hydrochloride* (8·1 g.) separated in long crimson prisms, m. p. 360—362° (Found: N, 15·0; Cl, 12·7. $C_{15}H_{16}N_3Cl$ requires N, 15·3; Cl, 13·0%). This hydrochloride dissolved in water giving a pale red solution having pH *ca.* 6·6; the solubility at 20° was *ca.* 3%. The hydrochloride (3 g.) was shaken with 2·5N-sodium hydroxide (100 c.c.) and glass beads for 1 hour and the light yellow insoluble base collected and washed. Recrystallisation from dilute alcoholic pyridine gave 5-*amino-*3-*dimethylaminoacridine* in stellate clusters of yellow needles, m. p. 256—258° (Found: C, 75·2; H, 6·3; N, 17·6. $C_{15}H_{15}N_3$ requires C, 75·9; H, 6·3; N, 17·7%). The base was very soluble in pyridine and almost insoluble in alcohol.

5-*Chloro-*4'-*dimethylaminodiphenylamine-*2-*carboxylic acid* (cf. Drozdov, *loc. cit.*). 2 : 4-Dichlorobenzoic acid (48 g.), potassium carbonate (41 g.), copper powder (1 g.), *p*-aminodimethylaniline (43 g.) and amyl alcohol (450 c.c.) were heated at 140° for 4 hours. The crude acid, isolated in the usual manner, was purified by reprecipitation and crystallisation

from the minimum amount of 96% alcohol; 5-chloro-4'-dimethylaminodiphenylamine-2-carboxylic acid was obtained in dark grey needles (36 g.). When recrystallised from the same solvent, it had m. p. 246—248° (Found: Cl, 12·0. Calc. for $C_{15}H_{15}O_2N_2Cl$: Cl, 12·2%).

5 : 8-*Dichloro-3-dimethylaminoacridine.* The foregoing acid (40 g.) was gently refluxed with phosphorus oxychloride (400 c.c.) for 4 hours and the resulting mixture, while still hot, slowly poured on to a large excess of powdered ice; ammonia was then added with stirring until the liquid was just alkaline, the temperature throughout being kept at < 2° by the addition of ice. The precipitate was separated from the cold liquor (vol. *ca.* 5 litres), washed, drained on porous porcelain and dried under reduced pressure at 20° over potassium hydroxide; the crude product (37 g.) was a deep red-brown powder. This was recrystallised from boiling benzene (*ca.* 400 c.c.) and gave 5 : 8-dichloro-3-dimethylaminoacridine (26 g.) in scarlet prisms, m. p. 200—202° (Found: N, 9·7; Cl, 24·5. Calc. for $C_{15}H_{12}N_2Cl_2$: N, 9·6; Cl, 24·4%). The compound is dichroic and may be obtained in brown leaves. When recrystallised from benzene–alcohol (3 : 1), it was obtained in long crimson needles, m. p. 206—208° (Found: Cl, 24·0%); a further sample crystallised from boiling alcohol–benzene–water (60 : 35 : 5) in scarlet prisms, m. p. 206—208° (Found: N, 9·6; Cl, 24·2%).

8-*Chloro-5-amino-3-dimethylaminoacridine.*—5 : 8-Dichloro-3-dimethylaminoacridine (10 g.) was heated with phenol (100 g.) for 1 hour at 110°, powdered ammonium carbonate (10 g.) slowly stirred in and the resulting solution heated at 110° for 2 hours and poured into an excess of dry ether. The precipitate was collected, dissolved in methanol (1500 c.c.), the solution refluxed for 2 hours and the solvent distilled away until the residual volume was *ca.* 750 c.c.; on cooling, 8-*chloro-5-amino-3-dimethylaminoacridine hydrochloride* (7·5 g.) separated in crimson needles, m. p. 368—370° (decomp.) (Found: N, 13·4; Cl, 22·8. $C_{15}H_{15}N_3Cl_2$ requires N, 13·7; Cl, 23·1%).

The hydrochloride (2 g.) was ground with 2N-sodium hydroxide (100 c.c.) and glass beads; the yellow base was collected, washed and recrystallised from dilute alcoholic pyridine giving 8-*chloro-5-amino-3-dimethylaminoacridine* in long golden needles, m. p. 304—306° (Found: N, 15·7; Cl, 13·2. $C_{15}H_{14}N_3Cl$ requires N, 15·5; Cl, 13·1%).

The authors thank Mr. H. S. Turner, B.Sc., for preparing the 3-acetamido-, 3-nitro-, 6-acetamido- and 6-nitro-derivatives of 2-chlorobenzoic acid and Mr. Fairbairn and Mr. R. Selway for technical assistance and some of the analytical work.

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## 30. *The Chloroacetylation of Guaiacol.*

By ALAN A. GOLDBERG and HAROLD S. TURNER.

Interaction of guaiacol, chloroacetic acid and phosphorus oxychloride at elevated temperatures yields principally 5-α*β-dichlorovinylguaiacol chloroacetate* and very little of the expected *5-chloroacetylguaiacol chloroacetate*; even at 100° appreciable amounts of the former are obtained. The orientation of the chief product has been ascertained by (i) hydrolysis and methylation, followed by the uptake of 3 mols. of hydrogen with formation of 2 mols. of hydrogen chloride and 4-ethylveratrole, (ii) ethylation and oxidation to *O*-ethyl*iso*vanillic acid. The 5-chloroacetylguaiacol chloroacetate was orientated by its hydrolysis and reduction to 5-ethylguaiacol, identified as its benzoate.

4-CHLOROACETYLGUAIACOL has previously been obtained in good yield by the interaction of veratrole and chloroacetyl chloride in the presence of aluminium chloride (Pratt and Robinson, *J.*, 1923, 753; cf. Tutin, *ibid.*, 1910, 2510) but there is no record of the direct production of the compound from guaiacol itself.

The acetylation of guaiacol yields products which depend largely upon the reaction conditions. Thus, 4-acetylguaiacol (acetovanillone) is obtained in 25% and 50% yields by the Fries rearrangement of guaiacol acetate in the presence of zinc chloride and aluminium chloride respectively, and the direct interaction of guaiacol and acetic acid in phosphoryl chloride solution at 100° gives 5-acetylguaiacol (*iso*acetovanillone) in a 20% yield (Coulthard, Marshall, and Pyman, *J.*, 1930, 280). Earlier, Reichstein (*Helv. Chim. Acta*, 1927, **10**, 392) had isolated 4-, 5-, and 6-acetylguaiacol from the rearrangement of guaiacol acetate with zinc chloride (cf. also Schneider and Kraft, *Ber.*, 1922, **55**, 1892).

During the course of synthesising Mannich bases containing a halogenated guaiacol residue it was observed that the interaction of guaiacol, chloroacetic acid and phosphorus oxychloride at elevated temperatures yields principally 5-α*β-dichlorovinylguaiacol chloroacetate* together with guaiacol chloroacetate and only a very limited amount of the expected *5-chloroacetylguaiacol chloroacetate*. These were separable by distillation. Even at 100° the dichlorovinyl derivative was formed in appreciable yield, although Krannichfeldt (*Ber.*, 1913, **46**, 4016) stated that guaiacol chloroacetate alone is formed under these conditions. Hydrolysis of the former with cold alkali gave 5-α*β-dichlorovinylguaiacol* the constitution of which was proved by methylation to 4-α*β-dichlorovinylveratrole* which on reduction with hydrogen and palladium-charcoal took up 3 mols. of hydrogen with formation of 4-ethylveratrole and liberation of 2 mols. of hydrogen chloride. Methylation of the αβ-dichlorovinylguaiacol followed by oxidation gave veratric acid whereas ethylation and oxidation yielded *O*-ethyl*iso*vanillic acid and this established the 5-position of the dichlorovinyl residue in the original dichlorovinylguaiacol. The orientation of the lesser product, 5-chloroacetylguaiacol chloroacetate, followed from its hydrolysis and reduction to 5-ethylguaiacol, identified as its benzoate.

It would appear that, by the reaction of the chloroacetic acid and phosphorus oxychloride on guaiacol, 5-chloroacetylguaiacol chloroacetate is initially formed and this, at the high temperature employed, is converted into 5-αβ-dichlorovinylguaiacol chloroacetate. This interpretation is supported by the yield of the 5-chloroacetylguaiacol chloroacetate being diminished and that of 5-αβ-dichlorovinylguaiacol chloroacetate being increased when the temperature is raised and the reaction time lengthened. The transformation may take place either by replacement of the hydroxyl group by chlorine in the *enol* form of the chloroacetylguaiacol

chloroacetate, R·C(OH):CHCl, or by formation of 5-ααβ-trichloroethylguaiacol chloroacetate by direct chlorination of the *keto* form of the chloroacetylguaiacol chloroacetate, R·CO·$CH_2$Cl, with subsequent cleavage of hydrogen chloride. The latter hypothesis would accord, except for the nature of the chlorinating agent, with the formation from acetophenone and phosphorus pentachloride of αα-dichloroethylbenzene which on distillation loses hydrogen chloride to yield α-chlorostyrene (Dyckerhoff, *Ber.*, 1877, **10**, 119); also compare the similar formation of αβ-dichlorostyrene from ω-chloroacetophenone (Friedel, *Ann. Chim. Phys.*, 1869, **16**, 360; Béhal, *Bull. Soc. chim.*, 1888, **50**, 632; Kunckell and Eras, *Ber.*, 1900, **33**, 3264).

An improved synthesis of *O*-ethyl*iso*vanillic acid is described.

## Experimental.

*Interaction of Guaiacol, Chloroacetic Acid, and Phosphorus Oxychloride.*—(*a*) *At* 170°. Guaiacol (75 g.), chloroacetic acid (200 g., 3·5 mols.) and phosphorus oxychloride (260 c.c., 5·5 mols.) were heated together in an oil-bath for 6 hours; the bath temperature, as the vigour of the reaction permitted, was raised from 110° to 170° over the first 3½ hours and then maintained at this temperature for 2½ hours. The product was cooled, poured on to an excess of powdered ice and the resulting liquor extracted three times with chloroform (900 c.c. in all). The chloroform extract was washed with dilute aqueous sodium bicarbonate and water, dried over calcium sulphate, the chloroform removed and the residual oil distilled. The fraction, b. p. 155—195°/0·3 mm. (92 g., 51%), consisting of 5-αβ-dichlorovinylguaiacol chloroacetate containing *ca.* 1% of 5-chloroacetylguaiacol chloroacetate, was collected. (In some experiments this was redistilled and the end fractions (3 g.) collected separately; the latter, on recrystallisation from benzene gave 5-chloroacetylguaiacol chloroacetate (*ca.* 0·5 g.), m. p. 130—134°). The crude product solidified on scratching and standing; it was recrystallised from ligroin (b. p. 40—60°)–diethyl ether (20 : 9 v/v) giving pure *5-αβ-dichlorovinylguaiacol chloroacetate* in silvery plates, m. p. 54—55° and b. p. 176—184°/0·5—0·6 mm., which very slowly turned pink (Found: C, 44·85; H, 3·3; Cl, 35·6. $C_{11}H_9O_3Cl_3$ requires C, 44·75; H, 3·1; Cl, 36·0%). The crude material was used for further work.

(*b*) *At* 150—155°. Guaiacol (75 g.), chloroacetic acid (143 g., 2·5 mols.) and phosphorus oxychloride (92 c.c., 2 mols.) were heated under reflux in an oil bath (150—155° bath-temp.) for 3 hours. The reaction mixture was treated as above and gave the following fractions: (i), b. p. 120—130°/1 mm. (74 g.), consisting of guaiacol chloroacetate; (ii), b. p. 125°/0·8 mm. to 185°/0·6 mm. (5·9 g.), a viscous liquid; (iii), b. p. 185—200°/0·6 mm. (13·3 g.), and (iv), b. p. 200—230°/0·6 mm. (11·3 g.), a viscous liquid depositing a white solid.

Fractions (iii) and (iv) were separately diluted with equal volumes of carbon tetrachloride; on remaining at 0°, these deposited colourless crystals of *5-chloroacetylguaiacol chloroacetate* (3·8 g.), m. p. 124—130°, and (6·3 g.), m. p. 132—134°, respectively. Recrystallisation of the combined crops from benzene gave 5-chloroacetylguaiacol chloroacetate in stout colourless needles, m. p. 133—134° (Found: C, 47·7; H, 3·8; Cl, 25·7; *M* (Rast), 281. $C_{11}H_{10}O_4Cl_2$ requires C, 47·7; H, 3·7; Cl, 25·6%; *M*, 277). Crude 5-αβ-dichlorovinylguaiacol chloroacetate was recovered from the first mother liquor.

4-*Chloroacetylguaiacol chloroacetate*, obtained from 4-chloroacetylguaiacol (Pratt and Robinson, *loc. cit.*) and chloroacetyl chloride in benzene solution, crystallised from ligroin–benzene in cream needles (Found: Cl, 26·2. $C_{11}H_{10}O_4Cl_2$ requires Cl, 25·6%). It had m. p. 93—95° which was depressed on admixture with the above 5-isomer.

(*c*) *At* 100°. Guaiacol (75 g.), chloroacetic acid (150 g., 2·6 mols.) and phosphorus oxychloride (200 c.c., 4·3 mols.) were heated on the water-bath for 4½ hours and the following fractions isolated as described above: (i), b. p. 125—130°/0·8 mm. (62 g.), consisted of guaiacol chloroacetate; it slowly solidified and, after crystallisation from ligroin, had m. p. 60°; (ii), b. p. 130—180°/0·7 mm. (5 g.), a viscous oil which deposited crystals of guaiacol chloroacetate on keeping; (iii), b. p. 180—220°/1·0 mm. (12·5 g.), a thick oil which slowly solidified, consisting chiefly of 5-αβ-dichlorovinylguaiacol chloroacetate.

*5-αβ-Dichlorovinylguaiacol.*—5-αβ-Dichlorovinylguaiacol chloroacetate (61 g.), dissolved in dioxan (400 c.c.), was added to 5N-sodium hydroxide (60 c.c., 1·5 equivalents) and the mixture gently warmed until a homogeneous solution was obtained. After the mixture had remained at 0° an equal volume of water was added, the solution acidified with 5N-sulphuric acid and extracted several times with ether (total, 1000 c.c.). The extract was dried over calcium sulphate, the ether removed and the residual oil distilled through a 14-cm. Vigreux column, the fraction, b. p. 140—142°/0·7 mm. (35·5 g.), being collected; this solidified on remaining at 0° and decomposed rapidly if not recrystallised at once. The solid (28·5 g.) on crystallisation from a mixture of ligroin (b. p. 40—60°) (100 c.c.), diethyl ether (15 c.c.) and benzene (5 c.c.) gave *5-αβ-dichlorovinylguaiacol* (22 g.) in colourless prisms, m. p. 55—56°, stable after drying over sodium hydroxide under reduced pressure but becoming pink on long storage. For analysis a sample was dried over phosphoric oxide at 45—50°/1 mm. (Found: C, 49·2; H, 3·6; Cl, 32·5. $C_9H_8O_2Cl_2$ requires C, 49·3; H, 3·7; Cl, 32·4%).

The following acyl derivatives were obtained by standard methods: *5-αβ-Dichlorovinylguaiacol acetate*, silvery plates from ligroin (b. p. 40—60°), m. p. 65·5—66·5° (Found: Cl, 27·0, 27·1. $C_{11}H_{10}O_3Cl_2$ requires Cl, 27·15%). *5-αβ-Dichlorovinylguaiacol* p-*toluenesulphonate*, stout colourless needles from ligroin (b. p. 60—80°), m. p. 94—96° (Found: C, 51·3; H, 3·8; Cl, 19·0. $C_{16}H_{14}O_4Cl_2S$ requires C, 51·5; H, 3·8; Cl, 19·0%). *5-αβ-Dichlorovinylguaiacol* p-*bromobenzenesulphonate*, fine colourless needles from ligroin (b. p. 60—80°), m. p. 95° (Found: 41·6; H, 2·5; Ag halide: substance, 1·096. $C_{15}H_{11}O_4Cl_2BrS$ requires C, 41·1; H, 2·6%; Ag halide: substance, 1·083). *5-αβ-Dichlorovinylguaiacol* m-*nitrobenzenesulphonate*, colourless plates from benzene–methanol, m. p. 84—85° (Found: C, 44·5; H, 2·85; Cl, 17·5. $C_{15}H_{11}O_6NCl_2S$ requires C, 44·5; H, 2·75; Cl, 17·55%).

*5-Chloroacetylguaiacol.*—When the crude and once distilled ester (62 g.), b. p. 155—195°/0·3 mm., was hydrolysed as above the crude phenol obtained on crystallisation from ligroin–ether–benzene yielded a small amount of white solid which had a very low solubility in the mixture. This was separately crystallised from benzene and gave long colourless needles (0·3 g.) of *5-chloroacetylguaiacol* (Found: C, 54·2; H, 4·6; Cl, 18·3. $C_9H_9O_3Cl$ requires C, 54·0; H, 4·5; Cl, 17·7%). It had m. p. 121—122°, depressed to 75—85° on admixture with 4-chloroacetylguaiacol (m. p. 102—104°, Pratt and Robinson, *loc. cit.*).

4-*αβ-Dichlorovinylveratrole.*—A solution of 5-αβ-dichlorovinylguaiacol (25 g.) in dry methanol (40 c.c.) was added to a solution of sodium (2·65 g.) in methanol (100 c.c.) followed by addition of methyl iodide (15 c.c.) and the resulting solution refluxed for 5 hours. The solvent was distilled away under reduced pressure, the residual oil mixed with water (50 c.c.) and extracted several times with ether (200 c.c. in all); the ethereal extract was treated with a small amount of sulphur dioxide to remove iodine, dried over potassium carbonate, the ether removed and the residual oil distilled. The fraction (22·9 g.), b. p. 147—149°/1 mm., was *4-αβ-dichlorovinylveratrole*; this was a pale yellow viscous oil which did not crystallise and decomposed slowly on keeping (Found: Cl, 30·6. $C_{10}H_{10}O_2Cl_2$ requires Cl, 30·5%). When dissolved in cold carbon tetrachloride, it did not take up bromine.

*Oxidation of* 4-*αβ-Dichlorovinylveratrole to Veratric Acid.*—The foregoing compound (9·5 g.) was rapidly stirred with water (150 c.c.) at 70—80° and a solution of potassium permanganate (29 g.) in water (350 c.c.) run in over 45 minutes.

The mixture was stirred for another hour at this temperature, basified with potassium hydroxide, filtered and the residue well washed into the filtrate. The latter was concentrated to *ca.* 200 c.c., acidified and kept at 0°; the precipitate was collected (2·5 g.) and crystallised from benzene, veratric acid being obtained in colourless needles, m. p. 180—182° alone and in admixture with an authentic specimen (Found: C, 59·7; H, 5·5; *M*, by titration, 181·5. Calc.: C, 59·4; H, 5·5%; *M*, 182).

*Hydrogenation of 4-αβ-Dichlorovinylveratrole to 4-Ethylveratrole.*—A solution of 4-αβ-dichlorovinylveratrole (5·0 g.) in ethanol (200 c.c.) and water (50 c.c.) was shaken in an atmosphere of hydrogen at 25°/800 mm. in the presence of a palladium catalyst prepared from palladium chloride (0·1 g.) and charcoal (10 g.). Absorption (1605 c.c. of hydrogen at 25°/744 mm.; calc.: (3 mols.) 1610 c.c.) was complete in 80 minutes. The catalyst was separated and washed with boiling water into the filtrate which required 56·7 c.c. of 0·778N-potassium hydroxide for neutralisation to phenolphthalein, corresponding to 0·0441 equivalents of hydrogen chloride (calc.: 0·0439 equivalents). The solutions from two hydrogenations were combined, the alcohol was removed, the residue extracted with ether, the extract dried and distilled. 4-Ethylveratrole (7·3 g.), b. p. 115—120°/14 mm., was obtained (Barger and Silberschmidt, *J.*, 1928, 2919, give b. p. 110—112°/9 mm.). On redistillation, 4·7 g. had b. p. 118—120°/14 mm. (Found: C, 72·35; H, 8·6. Calc.: C, 72·35; H, 8·5%).

The foregoing compound (3·5 g.) was stirred with water (80 c.c.) at 95° and potassium permanganate (24 g.) dissolved in boiling water (300 c.c.) added over 3 hours. The filtered solution was concentrated to *ca.* 100 c.c., acidified and strongly cooled. The colourless precipitate was crystallised from benzene (charcoal), yielding veratric acid (0·1 g.) in colourless needles, m. p. and mixed m. p. 180—182° (Found: *M*, 185).

*5-αβ-Dichlorovinylguaiacol Ethyl Ether.*—5-αβ-Dichlorovinylguaiacol (14·2 g.) dissolved in ethanol (40 c.c.) was added to a solution of sodium (1·4 g.) in alcohol (60 c.c.) followed by ethyl bromide (10 c.c.) and the mixture refluxed for 4 hours. After removal of the sodium bromide, the alcohol was removed, leaving an oil which slowly solidified. Crystallisation from ligroin (b. p. 80—100°) gave *5-αβ-dichlorovinylguaiacol ethyl ether* (9·6 g.) in colourless needles, m. p. 74—76° (Found: C, 53·6; H, 4·75; Cl, 28·4. $C_{11}H_{12}O_2Cl_2$ requires C, 53·5; H, 4·9; Cl, 28·7%).

O-*Ethylisovanillic Acid.*—The foregoing compound (8 g.) was stirred with water (200 c.c.) and a solution of potassium permanganate (15 g.) in water added during 1 hour; during the addition the temperature was maintained at 70—80° and the mixture then stirred for a further 1 hour. The crude acid, isolated in the usual manner, on crystallisation from benzene–toluene (4 : 1) gave *O*-ethyl*iso*vanillic acid (3 g.) in colourless needles, m. p. 164—166° alone and in admixture with the synthetic material from nitro-*p*-tolyl methyl ether described below (Found: C, 60·8; H, 5·9; *M*, by titration, 196·5. Calc.: C, 61·2; H, 6·2%; *M*, 196).

*Clemmensen Reduction of 5-αβ-Dichlorovinylguaiacol to 5-Ethylguaiacol.*—5-αβ-Dichlorovinylguaiacol (10 g.), amalgamated zinc (100 g.) and 3·3N-hydrochloric acid (300 c.c.) were refluxed for 10½ hours, benzene (80 c.c.) added and the whole refluxed for a further 7 hours. The layers were separated, the aqueous layer together with the residue extracted with benzene and the combined benzene solutions dried over calcium sulphate and distilled. 5-Ethylguaiacol (5·25 g.) was obtained as a colourless oil, b. p. 78—82°/2 mm., which solidified on strong cooling. Crystallisation from ligroin (b. p. 30—40°) gave the pure compound in colourless plates, m. p. 37·5—38·5 (lit., 35—36°) (Found: C, 70·6; H, 8·0. Calc.: C, 71·0; H, 8·0%). The benzoate had b. p. 175—180°/2 mm. and crystallised from ligroin (b. p. 40—60°) in large colourless prisms, m. p. 53·5—55·5° (lit., 53°) (Found: C, 75·0; H, 6·2. Calc.: C, 75·0; H, 6·3%). The *acetate* crystallised from ligroin (b. p. 30—40°) in colourless plates, m. p. 34—35° (Found: C, 67·6; H, 7·2. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%).

*Hydrolysis and Clemmensen Reduction of 5-Chloroacetylguaiacol Chloroacetate.*—5-Chloroacetylguaiacol chloroacetate (3 g.) was reduced by the Clemmensen method and the crude 5-ethylguaiacol (0·8 g., b. p. 124—125°/20 mm.) benzoylated in aqueous alkaline solution, the latter extracted with chloroform, the chloroform extract dried and distilled, the fraction b. p. 178—180°/2 mm. being collected (0·6 g.). This on crystallisation from ligroin (b. p. 40—60°) gave 5-ethylguaiacol benzoate in colourless prisms (0·45 g.), m. p. 53·5—55·5° alone and in admixture with a sample obtained from the reduction of 5-αβ-dichlorovinylguaiacol.

*2-Nitro-4-methylanisole.*—This was obtained from 2-nitro-4-methylphenol (53·5 g.) as described by Schultz (*Ber.*, 1907, **40**, 4324) but the crude product was distilled in superheated steam (oil bath temp. 200°); the 2-nitro-4-methylanisole distilled as a yellow oil (37 g.) in *ca.* 1 l. of distillate (cf. Brasch and Freyss, *Ber.*, 1891, **24**, 1960, and De Vries, *Rec. trav. chim.*, 1909, **28**, 284). The nitro compound (51 g.) was stirred on the water-bath with water (130 c.c.) and 10N-hydrochloric acid (5 c.c.) and finely divided iron powder ("Pacteron No. 2," 55 g.) added gradually during 2½ hours; more iron powder (20 g.) was then added and the stirring continued for another 2 hours. After the addition of saturated aqueous sodium carbonate (20 c.c.) the mixture was distilled in superheated steam (oil-bath temp. 200°). This distillate (2·5 l.) was saturated with sodium chloride, extracted with ether, the extract dried and distilled. 2-Amino-4-methylanisole (30 g.) distilled as an oil, b. p. 136—140°/29 mm., which solidified on cooling (cf. De Vries, *loc. cit.*, and Robinson, *J.*, 1916, 1088).

*5-Methylguaiacol.*—2-Amino-4-methylanisole (20 g.) dissolved in water (130 c.c.) and sulphuric acid (10·9 c.c.) was diazotised at 2° by the addition of a solution of sodium nitrite (11·5 g.) in water (37 c.c.). The diazo solution was added slowly to a solution of anhydrous sodium sulphate (115 g.) in water (87 c.c.) and sulphuric acid (87 c.c.) which, during the whole addition, was heated in an oil-bath (temp. 150° rising to 180°) and through which a current of dry steam was passing. The distillate (1·3 l.) was saturated with sodium chloride, repeatedly extracted with benzene (total, 250 c.c.), and the benzene solution dried and distilled. 5-Methylguaiacol (11·3 g.) distilled as a yellow oil, b. p. 83—86°/3 mm., which solidified to a mass of yellow plates (Limpach, *Ber.*, 1889, **22**, 350 and De Vries, *loc. cit.* give b. p. 222°/760 mm. and 180°/250 mm., respectively).

*5-Methylguaiacol Ethyl Ether.*—Ethyl sulphate (19 c.c.) was added in portions to a shaken solution of 5-methylguaiacol (13·4 g.) in water (30 c.c.) and 5N-sodium hydroxide (32 c.c.) heated on the water bath during 15 minutes. Heating was continued for a further 1½ hours, ammonia (20 c.c., *d* 0·880) added and the mixture distilled in steam. Ether extraction of the distillate followed by fractionation gave *5-methylguaiacol ethyl ether* as a colourless oil (13 g.) which, on redistillation, had b. p. 120°/30 mm. (Found: C, 72·5; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·35; H, 8·5%).

O-*Ethylisovanillic Acid.*—The foregoing ether (4·2 g.) was rapidly stirred with water (100 c.c.) at 90—95° and a boiling solution of potassium permanganate (12 g.) in water (150 c.c.) added slowly over 1½ hours; after heating at 90° for a further 1½ hours the product was isolated in the usual way. The crude acid (2·25 g.) was recrystallised from ligroin (b. p. 80—100°)–benzene (10 : 1) giving *O*-ethyl*iso*vanillic acid (1·8 g.) in colourless needles, m. p. 164—166° (Found: C, 61·3; H, 6·1; *M*, by titration, 194·5. Calc.: C, 61·2; H, 6·2%; *M*, 196).

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# 31. *The Preparation of Styrene Chlorohydrin.*

By W. E. Hanby and H. N. Rydon.

Methods for the conversion of styrene into styrene chlorohydrin have been studied; the best of these for preparative purposes is the reaction of styrene with *tert.*-butyl hypochlorite in dilute acetic acid. An improved method for the preparaton of *tert.*-butyl hypochlorite is described.

Styrene chlorohydrin (β-chloro-α-phenylethyl alcohol; Ph·CH(OH)·$CH_2$Cl) was first prepared by Detoeuf (*Bull. Soc. chim.*, 1922, **31**, 176), who obtained it by the action of monochlorourea on styrene in the presence of acetic acid; repetition of this work did not give the high yield (70%) claimed, the best yield in our experiments being only 52% (or 58%, allowing for recovered styrene). We therefore investigated a number of other reagents for the conversion of styrene into its chlorohydrin. The use of free hypochlorous acid for this purpose was not satisfactory; negligible yields were obtained by passing chlorine into suspensions of styrene in 10% sodium chloride solution at 90° (cf. the analogous preparation of styrene bromohydrin; Read and Reid, *J.*, 1928, 1487), in 8% sodium carbonate solution at 40—50°, or in water containing suspended calcium carbonate; somewhat better yields (32%; 36% allowing for recovered styrene) were obtained by adding dilute nitric acid to a stirred suspension of styrene in sodium hypochlorite solution (cf. the preparation of 2-chlorocyclohexanol; Coleman and Johnstone, *Org. Synth.*, 1925, **5**, 31).

A better reagent than monochlorourea for our purpose was found to be *tert.*-butyl hypochlorite, which has been used for the addition of hypochlorous acid to many olefins (Irwin and Hennion, *J. Amer. Chem. Soc.*, 1941, **63**, 858; Emling, Vogt, and Hennion, *ibid.*, p. 1624); using this reagent in dilute acetic acid, the yield of styrene chlorohydrin varied between 60% and 70% (73% and 84%, respectively, allowing for recovered styrene) and the process, described in detail below, appears to be the most convenient available for the preparation of the chlorohydrin.* Omission of the acetic acid in this preparation leads to the formation of the tert.-*butyl ether*, Ph·CH(OBu$^t$)·$CH_2$Cl, by direct addition; the p-*nitrobenzoate* and *acetate* of styrene chlorohydrin were also prepared and characterised. The purity of the various samples of styrene chlorohydrin was assessed by the yield of ω-chloroacetophenone obtained from them by chromic acid oxidation.

The original procedure of Chattaway and Backeberg (*J.*, 1923, **123**, 2999) for the preparation of *tert.*-butyl hypochlorite gave very variable yields in our hands; a modified method, employing calcium carbonate in place of sodium hydroxide and giving good and reproducible yields, is described below.

## Experimental.

*Preparation of Styrene Chlorohydrin.*—The following procedure gave the best yield of styrene chlorohydrin. Redistilled *tert.*-butyl hypochlorite (25 g.) was added during 1 hour to a stirred suspension of styrene (25 g.) in water (250 c.c.) and acetic acid (25 c.c.), the temperature being kept below 25° by cooling in ice. The reaction was complete after stirring for a further 15 mins.; the product was then extracted with ether, dried and distilled, yielding: (i) recovered styrene (4 g.), b. p. below 108°/6 mm.; (ii) styrene chlorohydrin (26·5 g.), b. p. 110—111°/6 mm., $d_4^{20\cdot5°}$ 1·1646, $n_D^{20\cdot5°}$ 1·5400, $[R_L]_D$ 42·16 (calc. 41·95) (Found: Cl, 22·2. Calc. for $C_8H_9OCl$: Cl, 22·7%). The yield was 70% (84% allowing for recovered styrene) and the material was of good quality, giving an 83% yield of ω-chloroacetophenone on oxidation. In another typical experiment using crude *tert.*-butyl hypochlorite (87 g.), styrene (92 g.), water (880 c.c.), and acetic acid (120 g.), the yield of chlorohydrin was somewhat lower (60%; 73% allowing for recovered styrene); the product gave a 77% yield of ω-chloroacetophenone on oxidation.

Omission of the acetic acid gave mainly the *tert.*-butyl ether of styrene chlorohydrin as indicated. Crude *tert.*-butyl hypochlorite (87 g.), styrene (92 g.), and water (1000 c.c.) were stirred for 2 hours at 15°. The lower layer was separated and distilled, yielding 40·8 g. of a fraction, b. p. 100—103°/5 mm., $n_D^{11°}$ 1·5234. This material (30 g.) was heated for 45 mins. at 120°/2 mm. with boric acid (0·88 g.) (cf. Schmidt, *Chem.-Ztg.*, 1928, **52**, 898); unreacted, non-hydroxylic material (b. p. 92—93°/2 mm.) was then distilled away. On redistillation impure β-tert.-*butoxy-β-phenyl-ethyl chloride* (β-chloro-α-phenylethyl *tert.*-butyl ether) (18·6 g.), b. p. 87—88°/1·5 mm., $d_4^{14°}$ 1·0549, $n_D^{14°}$ 1·5102, $[R_L]_D$ 60·27 (Calc. 60·53), was obtained (Found: Cl, 18·2. $C_{12}H_{17}OCl$ requires Cl, 16·7%). The product was contaminated with more highly chlorinated material which we were unable to remove.

*Derivatives of Styrene Chlorohydrin.*—*Styrene chlorohydrin* p-*nitrobenzoate* (β-chloro-α-phenylethyl *p*-nitrobenzoate), prepared in pyridine, crystallised from alcohol in parallelograms, m. p. 81° (Found: C, 59·1; H, 4·1. $C_{15}H_{12}O_4NCl$ requires C, 58·9; H, 3·9%).

The acetate was prepared by keeping styrene chlorohydrin (79 g.) with acetic anhydride (150 c.c.) for 1 hour at room temperature; the product was then refluxed for an hour, cooled, poured into water, and kept overnight. Distillation of the dried ether extract yielded *β-chloro-α-phenylethyl acetate* (65·8 g.; 66%) as an oil, b. p. 101—104°/3 mm., $n_D^{13°}$ 1·5182 (Found: C, 60·5; H, 5·8; Cl, 18·5. $C_{10}H_{11}O_2Cl$ requires C, 60·5; H, 5·5; Cl, 17·9%).

*Oxidation of Styrene Chlorohydrin.*—In a typical experiment, styrene chlorohydrin (26·5 g.) was added during 10 mins. to a stirred solution of sodium dichromate (35 g., 2·08 equivs.) in water (88 c.c.) containing sulphuric acid (17·5 c.c.). The temperature rose to 71°, falling again to 60° in 10 mins.; the stirred mixture was kept at 60° for 5 hours when it was poured on ice. The precipitated ω-chloroacetophenone was separated, washed, and dried in a vacuum desiccator (21·9 g., 84%; m. p. 51—53°).

*Preparation of* tert.-*Butyl Hypochlorite.*—Into a gently stirred suspension of calcium carbonate (50 g.) in water (1000 c.c.) containing *tert.*-butyl alcohol (74 g.) at 0—1° chlorine is passed until all the carbonate has dissolved (the rate of stirring is highly important; it should be just sufficient to keep the carbonate in suspension. If too fast, the yield falls considerably owing to hydrolysis). The upper layer is separated and washed once with water. This crude product

* Since this work was completed, early in 1942, an improved preparation of styrene chlorohydrin has been described by Emerson (*J. Amer. Chem. Soc.*, 1945, **67**, 516); Emerson's procedure appears to be more time-consuming than ours but may be preferable for large-scale working.

(87 g., 80%) is sufficiently pure for many purposes. Distillation gives pure *tert.*-butyl hypochlorite, b.p. 77—79° (65 g., 60%).

We are indebted to the Chief Scientific Officer, Ministry of Supply, for permission to publish this paper.

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## 32. *The Acetylation of Some 5-Aminoacridines.*

By J. H. WILKINSON and I. L. FINAR.

It has been shown that 5-aminoacridine forms a diacetyl derivative, as well as 5-acetamidoacridine (Albert and Goldacre, *J.*, 1943, 454). The orientation of the former has been studied, and the evidence obtained is in favour of structure (I). The acetylation of a number of substituted 5-aminoacridines has also been carried out, and a series of mono- and di-acetyl derivatives obtained.

DURING a study of the effect of fluorine substitution on the properties of 5-aminoacridine and similar compounds, a number of chlorine and methyl substituted 5-aminoacridines were acetylated by the method described by Albert and Goldacre (*loc. cit.*) for 5-acetamidoacridine. The 4-methyl derivative did not give the required acetyl compound, and a product was isolated which proved to be the diacetyl derivative. Later, it was found that 5-aminoacridine and a number of related compounds gave diacetyl derivatives, though somewhat more rigorous conditions than for 5-amino-4-methylacridine were found necessary.

The observation of Tschitschibabin and Bylinkin (*Ber.*, 1922, **55**, 998) on the dibenzoyl derivative of 2-aminopyridine seems relevant to the study of the structure of this new derivative of 5-aminoacridine. These authors point out that their compound may have either of the structures, (*a*) or (*b*).

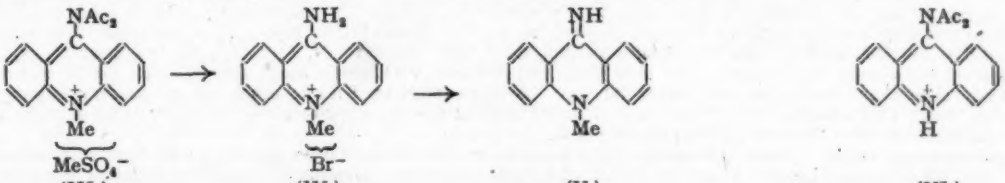
(*a*.) (*b*.)

(I.) (II.)

A similar reservation must be made in the case of the acridine derivative which may have either structure, (I) or (II).

It has been shown by Albert and Goldacre (*loc. cit.*) that in the case of the monoacetyl derivative of 5-aminoacridine the acetyl group is in the 5 position since, on treatment with methyl *p*-toluenesulphonate and subsequent hydrolysis, it gives 5-amino-10-methylacridinium bromide, (IV). Similarly, if the diacetyl derivative has structure (I), it should be possible to convert it to the quaternary salt (IV) by a similar series of reactions, whereas it is improbable that structure (II) would quaternise in view of the inductive effect exerted by the carbonyl groups on the " lone pair " electrons of the nitrogen atoms (Ingold, *Ann. Rep.*, 1926, **23**, 139).

When quaternisation with methyl *p*-toluenesulphonate [Albert and Goldacre (*loc. cit.*); Albert and Ritchie (*J.*, 1943, 458)] was attempted an unworkable black tar was obtained, but it was achieved by the use of dimethyl sulphate in nitrobenzene at 130°. The product (III), on hydrolysis with hydrobromic acid, gave 5-amino-10-methylacridinium bromide (IV), which, on treatment with alkali, gave 5-amino-5-hydroxy-10-methylacridan. When this was heated at 130°, 5-imino-10-methylacridan (V) was obtained. No reaction with methyl iodide occurred either with the diacetyl compound or with 5-acetamidoacridine.



(III.) (IV.) (V.) (VI.)

It is thus established that the structure of the diacetyl derivative is correctly represented by (I), but the possibility of molecular rearrangement, though remote, cannot be excluded.

All the acetyl derivatives dissolve in dilute mineral acid giving deep yellow solutions, thus indicating not only their basic nature, probably due to the ionic form (VI) (cf. Albert and Ritchie, *J.*, 1943, 458), but also the similarity in structure between the mono- and di-acetyl compounds.

Further confirmatory evidence based on a study of the ultra-violet absorption spectra of some of these compounds will be published elsewhere shortly by King, Gilchrist, and Tárnoky.

The formation of *5-diacetylaminoacridine* suggests that in the un-ionised state, 5-aminoacridine does not exist to any great extent in the imino form (see Craig and Short, *J.*, 1945, 419, for evidence from absorption spectra).

*The Fluorescence of the Acetyl Derivatives.*—None of the acetylated aminoacridines examined exhibited fluorescence in alcoholic solution by daylight but, in ultra-violet light, all were fluorescent, the colours and intensities varying according to the reaction of the solution. Under ultra-violet light, all the acetylated compounds showed a blue fluorescence in the solid state, *1-chloro-5-diacetylaminoacridine* being exceptionally vivid under these conditions.

## Experimental.

(M. ps. are corrected unless over 300°.)

*Preparation of Bases.*—Since this work was completed, Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169) have reported the preparation of the monomethyl- and monochloro-5-aminoacridines. The m. ps. reported are somewhat lower than those recorded in this paper, possibly because the former may be uncorrected. The corresponding 5-chloroacridines were converted to the 5-aminoacridines by the standard method (Albert and Ritchie, *Org. Syn.*, 1942, **22**, 5). The bases were isolated by precipitating the hydrochlorides with acetone, dissolving the latter in hot water and precipitating with sodium hydroxide. The yields varied from 80 to 90%.

1 : 5-*Dichloroacridine* was prepared by refluxing 2′-chlorodiphenylamine-2-carboxylic acid (Ullmann, *Annalen*, 1907, **355**, 312) (16 g.) with phosphorus oxychloride (35 c.c.) for 2 hours, followed by removal of the excess of the latter by distillation under reduced pressure. The residue was dissolved in chloroform, and washed free from acid with aqueous ammonia. The solvent was removed under reduced pressure. The product (14·9 g.) crystallised from a mixture of 90 parts of alcohol and 10 parts of 2N-ammonia in white plates, m. p. 100° (Found: N, 5·6. $C_{13}H_7NCl_2$ requires N, 5·6%).

1-*Chloro-5-aminoacridine* crystallised from 50% alcohol in small bright yellow prisms, m. p. 235° (Found: C, 68·2; H, 4·0; N, 12·5; Cl, 15·6. $C_{13}H_9N_2Cl$ requires C, 68·3; H, 3·9; N, 12·3; Cl, 15·5%). The *hydrochloride* was obtained as small lemon-yellow prisms, soluble in about 500 parts of water, m. p. over 360°, charring *ca.* 330° (Found: N, 10·45. $C_{13}H_9N_2Cl,HCl$ requires N, 10·6%).

2-Chloro-5-aminoacridine crystallised from chlorobenzene in small bright yellow prisms, m. p. 277° (U.S.P. 2,092,131 gives m. p. 277°). The *hydrochloride* crystallised in pale yellow plates, sparingly soluble in water, m. p. *ca.* 360° (decomp.) (Found: N, 10·25; Cl, 25·9. $C_{13}H_9N_2Cl,HCl,\frac{1}{2}H_2O$ requires N, 10·2; Cl, 25·9%).

3-Chloro-5-aminoacridine crystallised from chlorobenzene in small prisms, m. p. 288—289° (G.P. 364,035 gives 273—274° and U.S.P. 2,092,131 gives 269—270°) (Found: N, 12·2%). The *hydrochloride* was obtained as yellow rectangular prisms, soluble in about 1000 parts of water. It had m. p. over 360°, charring *ca.* 300° (Found: N, 10·75%).

4-*Chloro-5-aminoacridine* crystallised from chlorobenzene in small bright yellow prisms, m. p. 270° (Found: C, 67·8; H, 4·2; N, 12·4; Cl, 15·7%). The *hydrochloride* crystallised in lemon-yellow plates, soluble in about 150 parts water, m. p. 303° (corr., decomp.) (Found: N, 10·5%).

5-*Amino-3-methylacridine* crystallised from chlorobenzene in flat rectangular prisms, m. p. 252° (Found: C, 80·6; H, 5·6; N, 13·3. $C_{14}H_{12}N_2$ requires C, 80·75; N, 5·75; N, 13·5%). The *hydrochloride* was obtained in small lemon-yellow prisms, soluble in about 1000 parts of water, m. p. 328—329° (decomp.) (Found: N, 11·45. $C_{14}H_{12}N_2,HCl$ requires N, 11·4%).

5-*Amino-4-methylacridine* was prepared from 4-methylacridone (Gleu and Nitzsche, *J. pr. Chem.*, 1939, **153**, 200). It crystallised from 50% alcohol in small orange-yellow prisms, m. p. 248—249° (Found: C, 80·6; H, 6·0; N, 13·2%). The *hydrochloride* separated from acetone in small lemon-yellow prisms, soluble in about 30 parts of water, and highly soluble in alcohol. It had m. p. *ca.* 320° (decomp.) (Found: N, 11·1; Cl, 14·2. $C_{14}H_{12}N_2,HCl,\frac{1}{2}H_2O$ requires N, 11·05; Cl, 14·0%).

*Preparation of 5-Diacetylamino-4-methylacridine.*—5-Amino-4-methylacridine (1 g.) was heated at 105° for 30 minutes with acetic anhydride (2 c.c.) and allowed to cool. No precipitate was obtained on the addition of benzene, but in a repeat preparation, the reaction mixture was diluted with water (20 c.c.) and the resulting suspension neutralised with 2N-ammonia. The solid was separated, washed with water and dried at 90°. The *diacetyl derivative* crystallised from 50% alcohol in irregular white plates, m. p. 144° (Found: N, 9·6. $C_{18}H_{16}O_2N_2$ requires N, 9·7%).

*Preparation of Monoacetyl Derivatives.*—It was found that the other bases examined behaved in a similar manner to 5-aminoacridine when acetylated by the method of Albert and Goldacre (*loc. cit.*), although a larger proportion of acetic anhydride was found to facilitate the reaction. The base (4 g.) was heated at 105° in acetic anhydride (12 c.c.) for 30 minutes. After cooling, benzene (40 c.c.) was added and the solid separated, washed with alcohol and ammonia, and dried at 90°. The various 5-acetamidoacridines were crystallised from alcohol, the yields being of the order of 85 to 95%.

1-*Chloro-5-acetamidoacridine* crystallised from 90 volumes alcohol in long white needles, m. p. 267° (Found: N, 10·2. $C_{15}H_{11}ON_2Cl$ requires N, 10·35%). 2-*Chloro-5-acetamidoacridine* crystallised in cream–white, long feathery needles from 120 volumes alcohol, m p. 281° (Found: N, 10·4%). 3-*Chloro-5-acetamidoacridine* crystallised in pale yellow fine silky needles from 130 volumes alcohol, m. p. 297° (Found: N, 10·3%). 4-*Chloro-5-acetamidoacridine* crystallised in cream–white feathery needles from 45 volumes alcohol, m. p. 231° (Found: N, 10·4%). 5-*Acetamido-3-methylacridine* crystallised in colourless needles from 80 volumes alcohol, m. p. 268° (Found: N, 11·2. $C_{16}H_{14}ON_2$ requires N, 11·2%).

*Preparation of Diacetyl Derivatives.*—The base (2 g.) was refluxed with acetic anhydride (12 c.c.) for 30 minutes and, after cooling, the mixture was poured into water (30 c.c.). After neutralising with 2N-ammonia the product was separated, washed with water and dried at 90°. The crude diacetyl derivatives (yields 90—95%) were crystallised from aqueous alcohol. All were readily soluble in alcohol and benzene.

5-*Diacetylaminoacridine*. Large glistening white needles, m. p. 164°. These appear to be hydrated since, when heated at 130°/14 mm. for 2 hours, a loss in weight of 3·75% occurred. (*Hemihydrate* requires 3·15%). The *anhydrous* form crystallised from benzene in colourless hexagonal prisms, m. p. 164° (Found: C, 73·0; H, 5·1; N, 10·0. $C_{17}H_{14}O_2N_2$ requires C, 73·3; H, 5·05; N, 10·1%). Its orientation was verified by treatment of 1 g. with dimethyl sulphate (1 c.c.) in nitrobenzene (10 c.c.) at 130° for 30 minutes. After cooling, the mixture was treated with benzene (30 c.c.) and set aside. The precipitate was washed with benzene and dried. The crude methosulphate (1·25 g.) was dissolved in water (5 c.c.) and hydrolysed by heating at 90° with 48% hydrobromic acid (5 c.c.) for one hour. The solution was filtered (charcoal) and allowed to cool. The solid which separated was collected and crystallised from water, and proved to be 5-amino-10-methylacridinium bromide, m. p. 306—307° (decomp.) [Albert and Ritchie, *J.*, 1943, 458, give m. p. *ca.* 305° (decomp.)] (Found: N, 9·7. Calc. for $C_{14}H_{13}N_2Br$: N, 9·7%). The identity of this compound was confirmed by treatment with alkali to give the *pseudo*-base, which on drying at 130° gave the anhydro-base, 5-imino-10-methylacridan, m. p. 134—136° (Albert and Ritchie give m. p. 134—136°). A mixed m. p. with an authentic specimen showed no depression.

1-*Chloro-5-diacetylaminoacridine* was obtained in pale greenish–yellow square prisms, strongly fluorescent under ultra-violet light, m. p. 179·5° (Found: N, 9·1. $C_{17}H_{13}O_2N_2Cl$ requires N, 8·95%). 2-*Chloro-5-diacetylaminoacridine* was obtained in pale yellow regular parallelepipeds, m. p. 185° (Found: N, 8·8%). 3-*Chloro-5-diacetylaminoacridine* was obtained in colourless square prisms, m. p. 172° (Found: N, 9·0%). 4-*Chloro-5-diacetylaminoacridine* was obtained in

pale yellow plates, m. p. 155° (Found: N, 8·9%), and *5-diacetylamino-3-methylacridine* in pale yellow elongated rhombs m. p. 205° (Found: N, 9·8%).

*Fluorescence of Acetyl Derivatives under Ultra-violet Light.*

| | Base. | Monoacetyl derivative. | Diacetyl derivative. |
|---|---|---|---|
| (a) *In the solid state.* | | | |
| 5-Aminoacridine | Very faint green. | Blue. | Vivid blue. |
| 1-Cl-5-$NH_2$-acridine | Green | Blue | Vivid blue. |
| 2-Cl- ,, ,, | Absent. | Blue. | Blue. |
| 3-Cl- ,, ,, | Very faint green. | Blue. | Blue. |
| 4-Cl- ,, ,, | Green. | Blue. | Faint blue. |
| 5-$NH_2$-3-Me- ,, | Absent | Blue. | Blue. |
| 5-$NH_2$-4-Me- ,, | Absent. | — | Blue. |
| (b) *In alcoholic solution.* | | | |
| 5-Aminoacridine (acid) | Vivid blue. | Faint green. | Faint green. |
| ,, (neutral) | Vivid blue. | Blue. | Faint violet. |
| ,, (alkaline) | Green. | Faint green. | Faint green. |
| 1-Cl-5-$NH_2$-acridine (acid) | Blue. | Bluish green. | Faint blue. |
| ,, ,, (neutral) | Blue. | Blue. | Violet. |
| ,, ,, (alkaline) | Green. | Vivid green. | Vivid green. |
| 2-Cl-5-$NH_2$ ,, (acid) | Blue. | Green. | Very faint green. |
| ,, ,, (neutral) | Green. | Blue. | Violet. |
| ,, ,, (alkaline) | Green. | Vivid green. | Vivid green. |
| 3-Cl-5-$NH_2$ ,, (acid) | Blue. | Discharged. | Discharged. |
| ,, ,, (neutral) | Green. | Blue. | Violet. |
| ,, ,, (alkaline) | Green. | Vivid green. | Vivid green. |
| 4-Cl-5-$NH_2$ ,, (acid) | Blue. | Faint green. | Very faint green. |
| ,, ,, (neutral) | Green. | Blue. | Violet. |
| ,, ,, (alkaline) | Green | Vivid green. | Green. |
| 5-$NH_2$-3-Me ,, (acid) | Vivid blue. | Faint green. | Green. |
| ,, ,, (neutral) | Bluish-green. | Blue. | Violet. |
| ,, ,, (alkaline) | Bluish-green. | Vivid green. | Vivid green. |
| 5-$NH_2$-4-Me ,, (acid) | Vivid blue. | — | Green. |
| ,, ,, (neutral) | Blue. | — | Violet. |
| ,, ,, (alkaline) | Blue. | — | Vivid green. |

The authors wish to thank Mr. S. Bance, B.Sc., for the semi-microanalyses and Dr. H. J. Barber and the Directors of May and Baker Ltd. for facilities granted to one of us (J. H. W.).

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## 33. *The Reactivity of γ-Pyrone Quaternary Salts.*

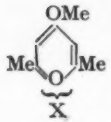
By R. M. Anker and A. H. Cook.

2 : 6-Dimethyl-4-pyrone methiodide or methoperchlorate possesses an unexpectedly labile methoxyl group. This grouping is readily exchanged for ethoxyl, and in presence of inorganic or organic tertiary bases it reacts intermolecularly with the formation of a binuclear dyestuff (II). With primary amines the quaternary salts may form 4-methoxy-2 : 6-lutidine quaternary salts but, under other conditions, the methoxyl group also enters into reaction to form substituted aminolutidine quaternary salts. With *sec.*-amines, reaction is limited to the formation of substituted aminopyrylium salts. This reactivity is not confined to amines and reaction with toluenethiol gives 4-benzylthio-2 : 6-dimethylpyrylium salts. The constitutions of these products have been confirmed by their conversion into pyridine derivatives.

The following work forms part of a broad survey of the chemistry of pyrones now in progress and originated in attempts to utilise the reactivity of the methyl groups in 2 : 6-dimethyl-4-pyrone in synthesising dyestuffs of cyanine character. This pyrone is known to condense with benzaldehyde to give 2 : 6-distyryl-4-pyrone (Boon, McKenzie, and Trotter, *Proc.*, 1914, **30**, 206) but preliminary attempts to condense it with *p*-dimethylaminobenzaldehyde, *p*-nitrosodimethylaniline, or 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde were unpromising and attention was turned to quaternary salts of the pyrone.

2 : 6-Dimethyl-4-pyrone methiodide and methoperchlorate have been prepared previously *via* the methosulphate (Kehrmann and Duttenhofer, *Ber.*, 1906, **39**, 1301; Baeyer, *Ber.*, 1910, **43**, 2337; Baeyer and Piccard, *Annalen*, 1915, **407**, 332). In the present investigation, it has not been possible to obtain these quaternary salts without the intermediation of dimethyl sulphate, and direct addition of methyl iodide or toluenesulphonic esters was not observed. Even using dimethyl sulphate, the reaction appeared to be complex and quantities of the pyrone acid sulphate were formed. On heating the pyrone with methyl iodide and a small quantity of dimethyl sulphate a considerable quantity of a red periodide was isolated; it coloured starch blue, gave the iodoform reaction with ethanol and caustic alkali, and was no doubt identical with the periodide, $C_7H_8O_2,HI,I_2$, described by Collie and Steele (*J.*, 1900, **77**, 1114).

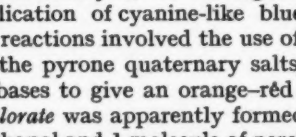
The constitution of these quaternary salts has been accepted as (I); the conversion of the perchlorate into 4-methoxy-2 : 6-lutidine (Baeyer, *loc. cit.*) provides convincing chemical evidence and formulation (I) is in agreement with the evidence of absorption spectra (Hantzsch, *Ber.*, 1919, **52**, 1535). The formation of 4-methoxypyridines from pyrone quaternary salts might seem to imply that the methoxyl group in (I) possesses only normal character, but it soon appeared that 2 : 6-dimethyl-4-pyrone methiodide and methoperchlorate contain a methoxy group of hitherto unsuspected lability.

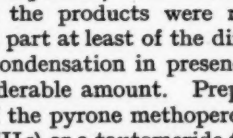


(I.)

When reaction between (I) and *p*-dimethylaminobenzaldehyde, 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde, or analogous anils (anilinovinyl compounds) was attempted, there was ample visual indication of cyanine-like blue and violet dyes but the products were not homogeneous. These attempted reactions involved the use of bases in the media and part at least of the difficulty was traced to the fact that the pyrone quaternary salts alone underwent self-condensation in presence of inorganic or organic tertiary bases to give an orange–red dyestuff in not inconsiderable amount. Prepared in methanol the *dyestuff perchlorate* was apparently formed from two molecules of the pyrone methoperchlorate by loss of 1 molecule of methanol and 1 molecule of perchloric acid. Structure (II*a*) or a tautomeride thereof (II*b*) seems to be the only one to accommodate these facts and account for the colour. In accordance with this formulation, (II) reacted readily with ammonia to give a colourless base formulated as the *derivative* (III*a* or III*b*).

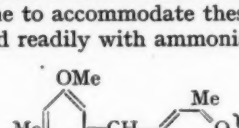
(II*a*.)

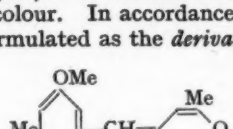




(II*b*.)

(III*a*.)



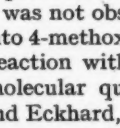


(III*b*.)

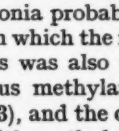
The formation of (II) was doubtless responsible for the observation of Baeyer and Piccard (*loc. cit.*) that the pyrylium salts (I) differ from analogous pyridinium salts in yielding no simple free base on treatment with alkali and in decomposing to give a red solution.

The formation of (II) postulates an unexpected ease of replacement of the methoxyl group in (I), but when this ease was appreciated, one reason for earlier difficulties in the purification of (II) and other products became apparent. Thus when the methoperchlorate (I) was recrystallised from ethanol the corresponding ethoperchlorate was obtained and this reverted to the methoperchlorate when crystallised from methanol; it seemed probable that exchange of radicals was taking place in other attempted condensations before reaction with the solvent and the consequent need for working only in methanol was recognised.

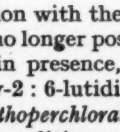
Formation of (II) was not observed with ammonia probably because reaction with the cyclic oxygen atom rapidly converts (I) into 4-methoxy-2 : 6-lutidine in which the methoxyl group no longer possesses any abnormal lability. Similarly reaction with primary amines was also very rapid and in presence, for example, of an approximately equimolecular quantity of aqueous methylamine, 4-methoxy-2 : 6-lutidine methiodide (IV; X = I) (cf. Conrad and Eckhard, *Ber.*, 1889, **22**, 73), and the corresponding *methoperchlorate* was also prepared. Compound (IV) underwent no further reaction with methylamine under the conditions used in these experiments. When, however, (I) was allowed to react with excess of methylamine in methanol the product contained



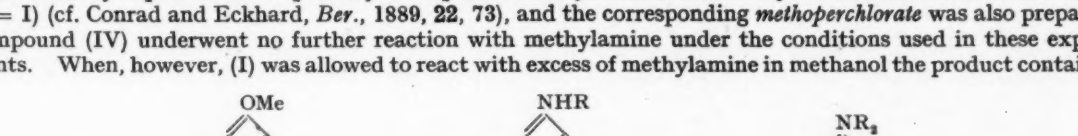
(IV.)



(V.)



(VI.)



(VII.) (VIII.)

2 atoms of nitrogen and must be formulated as 4-*methylamino*-2 : 6-*dimethylpyridine methoperchlorate* (V) (R = Me); when aniline was used instead of methylamine, two molecules of base were again introduced to give 4-*anilino*-2 : 6-*dimethylpyridine phenyl perchlorate* (V) (R = Ph).

These reactions can only be interpreted by assuming a ready replaceability of the methoxyl in (I). If conditions are such that reaction of the methoxyl can take precedence over that with the oxonium oxygen, full reaction is completed by the formation of compounds of type (V); if, however, reaction is initiated at the

oxonium oxygen, the primary product has no special further reactivity and the product is of type (IV). If this be the case, reaction of (I) with secondary amines presents particular interest in that completion of reaction by formation of pyridine derivatives becomes impossible and reaction should cease with formation of amino-pyrylium salts (VI).

This hypothesis was confirmed by allowing (I) to react with a variety of secondary amines and isolating in good yield 4-N-*piperidyl*-2 : 6-*dimethylpyrylium iodide* and *perchlorate*, 4-*diethylamino*-2 : 6-*dimethyl*- and N-*morpholinyl*-2 : 6-*dimethyl-pyrylium iodide*. Piperazine underwent two-fold reaction with formation of *piperazine*-NN′-*bis*-2 : 6-*dimethylpyrylium perchlorate*. The constitution of these compounds was in no doubt since the piperidyl compound (VII) reacted with ammonia to give 4-N-*piperidyl*-2 : 6-*lutidine* (VIII); the latter was synthesised independently from 2 : 6-dimethyl-4-pyrone *via* 2 : 6-dimethyl-4-pyridone and 4-chloro-2 : 6-lutidine which reacted with piperidine to give (VIII), identical with the material obtained earlier. The difficulty with which even 4-chloro-2 : 6-lutidine reacted with piperidine was in marked contrast with the ease of reaction of (I) with piperidine and emphasised the highly reactive nature of its methoxyl group. Compound (VII) also reacted with methylamine to give 4-N-*piperidyl*-2 : 6-*lutidine methoperchlorate*.

The above transformations suggested that (I) and similar compounds would eliminate alcohols on reaction with more diverse compounds containing " reactive " hydrogen, methin, methylene, or methyl groups. In preliminary experiments (I) was allowed to react in boiling methanol with toluenethiol when 4-*benzylthio*-2 : 6-*dimethylpyrylium perchlorate* was formed. This constitution was confirmed by its giving with ammonia the base, 4-*benzylthio*-2 : 6-*lutidine*; this was also obtained from toluenethiol and 4-chloro-2 : 6-lutidine, the products from the two routes being identified as the *picrate*.

From a theoretical viewpoint this reactivity can be regarded only as a manifestation of the relative reluctance of an oxonium group to contribute to a resonating aromatic system with consequent resemblance of the ring structure in (I) to an olefinic system. Practically, the reactivity of γ-pyrone quaternary salts exemplified above provides routes to many types of compound of general interest and the further examination of these possibilities in the pyrone and chromone fields is in progress.

## Experimental.

2 : 6-Dimethyl-4-pyrone (31 g.), dimethyl sulphate (43 g.), and methanol (4 c.c.) were warmed to 55—60° and the homogeneous melt cooled and stirred with sodium iodide (150 g.) in water (100 c.c.). After 2 hours, the solid was collected and washed with acetone. The residue consisted of the pyrone methiodide which decomposed with effervescence at 110°. The acetone washings contained the pyrone hydriodide and turned brown on standing in air. On evaporating the washings crystals of 2 : 6-dimethyl-4-pyrone periodide (Collie and Steele, *loc. cit.*) were deposited; the compound separated from ethyl acetate in stout red needles, m. p. 114° (Found : C, 27·1; H, 2·8; available I, 39·4. Calc. for $C_{14}H_{17}O_4I_3$ : C, 26·9; H, 2·7; available I, 40·3%). 2 : 6-Dimethyl-4-pyrone methoperchlorate was prepared according to Baeyer and Piccard (*loc. cit.*), but sodium perchlorate was used instead of perchloric acid; the methoperchlorate could be recrystallised from methanol without serious loss. On crystallising the methoperchlorate from ethanol, the corresponding ethoperchlorate was obtained. It separated in needles, m. p. 124° (the methoperchlorate has m. p. 195°), which were more soluble in chloroform than the methoperchlorate (Found : C, 43·0; H, 4·9. Calc. for $C_9H_{13}O_6Cl$ : C, 42·8; H, 5·2%) (Meerwein and Coll, *J. pr. Chem.*, 1937, **147**, 257). The ethoperchlorate dissolved in *n*- or *iso*-propanol on standing for several days but, on evaporating the solutions, perchlorates resulted which could not be obtained pure and which were not reconverted into the methoperchlorate by refluxing in methanol. The methoperchlorate remained apparently unchanged on refluxing in *n*- or *iso*-propanol or fusing at 100° for 30 mins. with phenol.

2 : 6-Dimethyl-4-pyrone methoperchlorate (20 g.), anhyd. sodium acetate (3·5 g.), and methanol (200 c.c.) were refluxed for 15 mins. The solution became deep red almost immediately. On cooling, the solid was collected and recrystallised from methanol; the *dyestuff perchlorate* (II) (10·4 g.) separated in small red-brown prisms which decomposed violently at *ca.* 260° (Found : C, 52·5; H, 4·95. $C_{15}H_{17}O_7Cl$ requires C, 52·2; H, 5·0%). The same material was formed on warming the methoperchlorate (2·5 g.), triethylamine (1·1 g.), and methanol (40 c.c.), removing the unchanged salt which separated on cooling, and evaporating the filtrate and digesting the residue with water. It was also obtained by using diethylaniline in place of triethylamine. It did not appear to condense with *p*-dimethylaminobenzaldehyde. The compound dyed cotton a pale pink, and cotton mordanted with antimony brown, but the dyeings were unstable to hot aqueous sodium carbonate; aqueous solutions of the dye were, however, apparently unaffected by acid or alkali. The dyestuff perchlorate (10·2 g.) was heated in a closed flask with ammonia solution (30 c.c., *d* 0·880) at 70° for 3 hours. On cooling, a base separated in prisms and more was obtained by extracting the mother liquor with chloroform. The *derivative* (III) separated from toluene in prisms, m. p. 186° (Found : C, 74·05; H, 6·8; N, 5·95. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·05; N, 5·75%).

*Reactions with primary amines.* 2 : 6-Dimethyl-4-pyrone methiodide (4·0 g.) was heated in a sealed tube for 30 mins. at 80° with ethanol (10 c.c.) and methylamine (0·7 g.). On evaporating and recrystallising the product from ethanol, 4-methoxy-2 : 6-lutidine methiodide (0·8 g.) separated in prisms, m. p. 204° (cf. Conrad and Eckhard, *loc. cit.*) (Found : C, 39·3; H, 5·1; N, 4·7. Calc. for $C_9H_{14}ONI$ : C, 38·7; H, 5·05; N, 4·4%); it was identical with the product of quaternising 4-methoxy-2 : 6-lutidine with methyl iodide. When the pyrone methoperchlorate (2·4 g.) was added to methylamine carbonate (3 g.) in water (15 c.c.), heat was evolved and after warming and shaking for 20 mins., pptn. commenced and was completed by adding sodium perchlorate. Recrystallisation from methanol gave the corresponding 4-*methoxy*-2 : 6-*lutidine methoperchlorate*, which separated in needles, m. p. 187° (Found : C, 42·9; H, 5·6. $C_9H_{14}O_5NCl$ requires C, 42·9; H, 5·6%). It was identical with the perchlorate obtained by quaternising 4-methoxy-2 : 6-lutidine with methyl iodide and salting out the product from aqueous solution with sodium perchlorate. From the methanolic mother liquors 4-*methylamino*-2 : 6-*lutidine methoperchlorate* separated in octahedra, m. p. 224° (Found : C, 43·2; H, 6·1; N, 10·95. $C_9H_{15}O_4N_2Cl$ requires C, 43·1; H, 6·1; N, 11·2%). The latter was the main product (4 g.) when 2 : 6-dimethyl-4-pyrone methoperchlorate (5 g.) was warmed with methylamine (2 g.) in methanol (50 c.c.) at 70° for 15 mins. 2 : 6-Dimethyl-4-pyrone methoperchlorate (3·0 g.), methanol (20 c.c.), and aniline (1·2 g.) were refluxed for 1 hour and the solution evaporated. The cryst. deposit was recrystallised from ethyl acetate–methanol (5 : 1) and then from methanol when 4-*anilino*-2 : 6-*dimethylpyridine phenyl perchlorate* separated in rhombic plates, m. p. 222° (Found : C, 60·6; H, 5·2; N, 7·9. $C_{19}H_{18}O_4N_2Cl$ requires C, 60·9; H, 5·2; N, 7·5%).

*Reactions with secondary amines.* 2 : 6-Dimethyl-4-pyrone methiodide (2·7 g.) was refluxed for 15 mins. in ethanol

(30 c.c.) with piperidine (0·9 g.) and the solution allowed to evaporate. The crystals were collected and crystallised from ethanol when 4-N-*piperidyl*-2 : 6-*dimethylpyrylium iodide* separated in prisms, m. p. 188—190° (Found : C, 44·5; H, 5·6; N, 4·4. $C_{12}H_{18}ONI$ requires C, 45·1; H, 5·7; N, 4·4%). When the corresponding pyrone methoperchlorate was treated similarly 4-N-*piperidyl*-2 : 6-*dimethylpyrylium perchlorate* (yield, 65%) was obtained. It separated from ethanol in prisms, m. p. 145° (Found : C, 49·5; H, 6·2. $C_{12}H_{18}O_5NCl$ requires C, 49·4; H, 6·25%). The preceding compound (4 g.), ammonium carbonate (4 g.), 10% aqueous ammonia (30 c.c.), and methanol (20 c.c.) were warmed until solution was complete, water (100 c.c.) added and the base extracted with chloroform. Evaporation and recrystallisation of the residue from ligroin gave 4-N-*piperidyl*-2 : 6-*dimethylpyridine* (2 g.) which separated in octahedra, m. p. 83° (Found : C, 75·5; H, 9·3; N, 14·6. $C_{12}H_{19}N_2$ requires C, 75·7; H, 9·6; N, 14·7%). 2 : 6-Dimethyl-4-pyrone (20 g.) and ammonia solution (30 c.c., *d* 0·880) were heated for 12 hours at 120° and the product evaporated to dryness. The residue was treated with phosphorus oxychloride (30 c.c.) and phosphorus pentachloride (37 g.) and reaction completed by refluxing. Evaporation, addition of excess of sodium hydroxide to the residue and extraction with ether gave 4-chloro-2 : 6-dimethylpyridine (17·2 g.), b. p. 177—178° (cf. Conrad and Epstein, *Ber.*, 1887, **20**, 162). The last compound (2·8 g.) was heated with piperidine (3·6 g.) for 2 hours at 150°, the cold product poured into excess of sodium hydroxide, and the bases extracted with ether. Distillation removed much unchanged chlorolutidine and the solid 4-*N*-piperidyllutidine was recrystallised from ligroin when it separated in octahedra, m. p. 82°, giving no depression in m. p. when mixed with the product prepared earlier. The identity was confirmed by the formation of the same *picrate* which separated from ethanol in prisms, m. p. 149—150° (Found : C, 52·0; H, 4·9; N, 16·5. $C_{18}H_{21}O_7N_5$ requires C, 51·6; H, 5·0; N, 16·7%); it was accompanied by a second picrate which was separated from the first by flotation in ligroin and which formed prisms, m. p. 151°, from benzene, depressing the m. p. of the first compound. 4-*N*-Piperidyl-2 : 6-dimethylpyrylium perchlorate (3·5 g.) was added to 33% methylamine in ethanol (3 g.); the initial reaction was moderated by cooling and completed at 80° (sealed tube) for 20 mins. On evaporation, 4-N-*piperidyl*-2 : 6-*lutidine methoperchlorate* was obtained. It separated from ethanol in prisms (2·2 g.), m. p. 178—179° (Found : C, 51·4; H, 6·6. $C_{13}H_{21}O_4N_2Cl$ requires C, 51·2; H, 6·9%).

The following were prepared by method used for the above piperidylpyrylium salt : 4-*diethylamino*-2 : 6-*dimethylpyrylium iodide*, plates, m. p. 192°, from ethanol (Found : C, 42·85; H, 5·75. $C_{11}H_{18}ONI$ requires C, 43·0; H, 5·9%); 4-N-*morpholinyl*-2 : 6-*dimethylpyrylium iodide*, prisms, m. p. 213°, from ethanol (Found : C, 41·3; H, 5·1. $C_{11}H_{16}O_2NI$ requires C, 41·1; H, 5·05%). Piperazine hydrate (0·8 g.), 2 : 6-dimethyl-4-pyrone methoperchlorate (3·6 g., 2 mols.), and ethanol (60 c.c.) were refluxed for 15 mins. and the solution cooled. The product (2·0 g.) was crystallised from glycol monomethyl ether–ethanol (1 : 1) and then from glycol monomethyl ether alone when *piperazine*-NN′-*bis*-2 : 6-*dimethylpyrylium perchlorate* separated in small prisms which exploded at *ca.* 260° (Found : C, 42·9; H, 4·7. $C_{18}H_{24}O_{10}N_2Cl$ requires C, 43·3; H, 4·8%).

2 : 6-Dimethyl-4-pyrone methoperchlorate (2·4 g.) was refluxed for 90 mins. with methanol (20 c.c.) and toluenethiol (1·3 g.) and the solution cooled to 0°. Unchanged dimethylpyrone methoperchlorate was separated and the mother liquor, on evaporation, gave 4-*benzylthio*-2 : 6-*dimethylpyrylium perchlorate* (0·7 g.) which crystallised from methanol in platelets, m. p. 146° (Found : C, 51·0; H, 4·65. $C_{14}H_{15}O_5ClS$ requires C, 50·85; H, 4·6%). This salt was warmed with ammonium carbonate (2 g.) and aqueous ammonia (10 c.c., 15%) until the solid had become quite oily, the oil extracted with ether and converted into its picrate. It formed needles, m. p. 171—172°, from methyl ethyl ketone–ethanol (1 : 4) giving no depression in m. p. when mixed with the picrate of 4-benzylthio-2 : 6-lutidine prepared as follows. 4-Chloro-2 : 6-lutidine (3 g.) and toluenethiol (2·5 g.) were heated (sealed tube) for 4 hours at 200°, the oil taken up in 2N-hydrochloric acid and the solution extracted with ether. The aqueous layer was basified with sodium carbonate and the liberated base taken up in ether and distilled. 4-*Benzylthio*-2 : 6-*lutidine* (3·5 g.) was obtained as an oil, b. p. 260°/25 mm. (Found : C, 73·3; H, 6·6. $C_{14}H_{15}NS$ requires C, 73·3; H, 6·6%). The *picrate* separated from methyl ethyl ketone–ethanol (1 : 4) in needles, m. p. 171—172°, identical with that described above (Found : C, 52·35; H, 3·85. $C_{20}H_{16}O_7N_4S$ requires C, 52·4; H, 3·95%).

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W.7 [*Received, November 15th,* 1945.]

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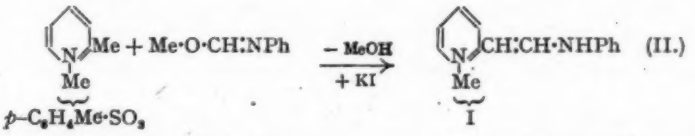
## 34. *Reactions of Alkylisoformanilides. Part II. Reactions with Pyridinium Salts.*

By EDWARD B. KNOTT.

Alkyl*iso*formanilides will react with quaternary salts of mono- and poly-methylpyridines thereby converting the 2- and 4-methyl group to a β-anilinovinyl group. 2 : 6-Dimethylpyridinium salts also yield 2 : 6-*di*-β-*anilinovinylpyridinium salts.*

THE preparation of β-acetanilidovinyl or β-anilinovinyl derivatives of cyclic quaternary ammonium salts, useful as intermediates in the preparation of photographic sensitising dyes, is usually achieved by the condensation of the ammonium salt containing a reactive methyl group with diphenylformamidine in acetic anhydride or by fusion (Piggott and Rodd, B.P. 344,409). Various examples of such compounds have been described in this and other patents, but only a few analogous compounds derived from homologues of pyridine have been described. α-Picolinium salts react readily on fusion with diphenylformamidine (Ogata, *J. Chem. Soc. Japan*, 1934, **55**, 394), giving the desired derivative, but before this application was attempted a more satisfactory alternative method of preparing such β-anilinovinyl derivatives had been found. Kuhn and Kern (B.P. 334,706) described the condensation of quaternary ammonium salts containing a reactive methyl group with substances of the general type, R·N:CR′X (I), where R and R′ represent hydrogen, alkyl, aralkyl or aryl groups and X is amino, alkoxy, acyloxy or halogen. Such substances are said to yield acetamidovinyl or acetanilidovinyl or substituted derivatives of the quaternary salt, on condensation in acetic anhydride. In the final specification, however, Kuhn and Kern restricted the general formula, (I), to substances where R and R′ are hydrogen, presumably because the larger general formula included substances which either do not condense or

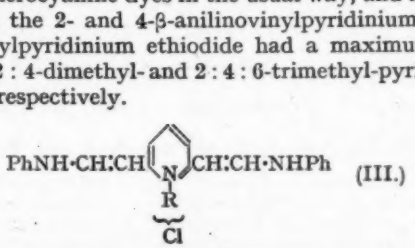
do not give the desired product. Included in this larger group are the alkyl*iso*formanilides (I; R = Ph, R′ = H; X = alkoxy). When these substances were allowed to react with quaternary salts of quinaldine, 2-methylbenzthiazole and similarly constituted bases in acetic anhydride the only products obtainable were carbocyanine dyes. When acetic anhydride–acetic acid was employed as solvent, as recommended in the above patent, the required β-acetanilidovinyl derivatives were obtained; this was not unexpected since, as has been shown in Part I (*J.*, 1945, p. 687) an alkyl*iso*formanilide is converted rapidly and probably quantitatively into diphenylformamidine acetate on contact with acetic acid. The formation of the acetanilidovinyl derivative then results from the reaction of the quaternary salt and the above acetate as indicated in B.P. 344,409. With α-picolinium salts the use of acetic anhydride–acetic acid gave only a low yield of the β-acetanilidovinyl derivative. It was found, however, that reaction in a solvent which did not react with the anilino group, *e.g.* alcohols, gave very high yields of the required 2-β-anilinovinyl derivatives of benzoxazolium, benzthiazolium, naphthathiazolium and other salts. This reaction was applied to the quaternary salts of pyridines containing reactive methyl groups. On refluxing in ethyl alcohol a molar mixture of 2-methylpyridine metho-*p*-toluenesulphonate and methyl*iso*formanilide the reaction mixture yielded the required 2-β-anilinovinylpyridine methiodide (II) on treatment with potassium iodide.



(II.)

The corresponding *ethiodide* was formed in the same way. The yields, however, were *ca.* 30%. These low yields were due to a low reaction temperature and, on changing the solvent to *n*-butyl alcohol or pyridine, the yield was raised to 50%. In *n*-amyl alcohol the yield was 60% and, finally by fusion at 160°, the yield was raised to over 70%. By dissolving in hot acetic anhydride the anilino group was readily acetylated yielding 2-β-*acetanilidovinylpyridine alkiodides* which are extremely soluble in water. The isomeric 4-β-*anilinovinylpyridine alkiodides* obtained in the same way from γ-picoline alkyl *p*-toluenesulphonates were similar in colour to the 2-isomers (maximum absorption at 405 and 400 mμ respectively) but were more water-soluble.

In the preparation of mono-β-anilinovinyl derivatives from pyridines containing more than one reactive methyl group the mildest possible condensation conditions, compatible with a reasonable yield, are necessary in order to avoid the simultaneous formation of di-β-anilinovinyl derivatives. The formation of the mono-derivative is aided, however, in the case of pyridines containing 2- and 4-methyl groups by the higher reactivity of the former. In the case of 2 : 6-dimethylpyridine the two methyl groups are of identical reactivity. The best reaction temperature was found to be that of boiling *n*-butyl alcohol. By the use of this solvent the 2-β-*anilinovinyl*-6-*methylpyridinium* salts were obtained and isolated as their p-*toluenesulphonates* which are less soluble than the chlorides. 2-β-*Anilinovinyl*-4-*methylpyridinium* salts gave the p-*toluenesulphonates* as oils, but the *methobromide* was crystalline. 2-β-*Anilinovinyl*-4 : 6-*dimethylpyridinium* salts were isolated as their *metho*-p-*toluenesulphonates* and *ethiodides*. The position of the β-anilinovinyl group was determined by conversion of the derivative to dimethinmerocyanine dyes in the usual way, and a comparison of the absorption of these dyes with those obtained from the 2- and 4-β-anilinovinylpyridinium salts. The dye obtained from 3-ethylrhodanine and 4-β-anilinovinylpyridinium ethiodide had a maximum absorption at 563 mμ whilst similar dyes obtained from 2-methyl-, 2 : 4-dimethyl- and 2 : 4 : 6-trimethyl-pyridinium ethiodides had maximum absorptions at 538, 546, and 543 mμ respectively.



(III.)

Attempts to prepare di-β-anilinovinyl derivatives were successful only from 2 : 6-dimethylpyridine. 2 : 6-*Di*-β-*anilinovinylpyridine methochloride* (III; R = Me) and *ethochloride* (III; R = Et) were readily obtained on fusing the reactants at 170—200°. Their alcoholic solutions showed an intense green fluorescence. The methochloride crystallised in long threads giving a gel-like consistency to the crystallising liquor. Acetylation of the methochloride gave 2 : 6-*di*-β-*acetanilidovinylpyridine methochloride* in a crystalline state on adding ether to the acetic anhydride solution. The corresponding ethochloride was not obtained crystalline.

## Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford; m. ps. are uncorrected.)

*2-β- and 4-β-Anilinovinylpyridinium Salts.*—2-Methylpyridine or 4-methylpyridine (3·72 g., 0·04 mol.) and methyl *p*-toluenesulphonate (7·44 g., 0·04 mol.) or ethyl *p*-toluenesulphonate (8·0 g., 0·04 mol.) were fused for 15 minutes at 100°. Methyl*iso*formanilide (5·4 g., 0·04 mol.) or ethyl*iso*formanilide (6·0 g.) was added and fused at 160° for 30 minutes. Alcohol was evolved and the melt turned orange. Alcohol (10 c.c.) was added to give a mobile liquid which was then poured into aqueous potassium iodide. The methiodide and ethiodide of the 2-isomer crystallised immediately as did also the methiodide of the 4-isomer. The ethiodide of the latter isomer separated as an oil which solidified slowly. 2-β-Anilinovinylpyridine methiodide, recrystallised from water, formed long glistening yellow needles, m. p. 210—212°

softening at 204° (Found : N, 8·6; I, 37·4. Calc. for $C_{14}H_{15}N_2I$ : N, 8·3; I, 37·55%). Ogata (*loc. cit.*) gives m. p. 203°. The *perchlorate*, from water, formed orange needles, m. p. 196—197° (Found : N, 8·85. $C_{14}H_{13}O_4N_2Cl$ requires N, 9·0%).

2-β-Acetanilidovinylpyridine methiodide was obtained by refluxing the methiodide in acetic anhydride for 15 minutes and precipitating with ether. From aqueous potassium iodide, it formed pale yellow clusters of needles, m. p. 204°, containing water of crystallisation, removed by drying at 150° for 3 hours. Ogata (*loc. cit.*) gives m. p. 177° (Found : I, 33·5. Calc. for $C_{16}H_{17}ON_2I$ : I, 33·4%). The *methoperchlorate* from water formed jagged, orange plates, m. p. 198—200° (Found : N, 7·95. $C_{16}H_{17}O_5N_2Cl$ requires N, 7·95%). *2-β-Anilinovinylpyridine ethiodide* was obtained as the *monohydrate* from water, m. p. 206—207°, with previous shrinking (Found : N, 7·65. $C_{15}H_{19}N_2I,H_2O$ requires N, 7·55%). Dried at 137° over potassium hydroxide at 20 mm., the *anhydrous* salt was obtained, m. p. 206—207° (Found : N, 8·05; I, 35·95. $C_{15}H_{17}N_2I$ requires N, 7·9; I, 35·85%). The *ethoperchlorate* formed yellow needles, m. p. 161—162°, from water (Found : N, 8·5. $C_{15}H_{17}O_4N_2Cl$ requires N, 8·65%). The acetylated methiodide formed an oil which solidified under dry ether. It was not purified.

*4-β-Anilinovinylpyridine methiodide*, recrystallised from water, formed glistening flat yellow needles, m. p. 196° (Found : I, 37·4. $C_{14}H_{15}N_2I$ requires I, 37·55%). *4-β-Anilinovinylpyridine ethiodide trihydrate* was difficult to purify. The crude solid was washed with a little *iso*propyl alcohol–ice water (5 : 1) to remove a dark colouring matter, dissolved in water at 20° and sufficient aqueous potassium iodide added to give a slight turbidity. On cooling to 5°, it crystallised as glistening flat yellow needles, m. p. 64—66° (Found : I, 31·15. $C_{15}H_{17}N_2I,3H_2O$ requires I, 31·25%).

*2-β-Anilinovinyl Derivatives of Polymethylpyridines.*—The pyridine (1 mol.) and alkyl *p*-toluenesulphonate (1 mol.) were fused at 100° for 15 minutes. Methyl*iso*formanilide (1 mol.) and sufficient *n*-butyl alcohol for solution were added and refluxed for 1 hour. The mixture was then poured into water or aqueous potassium bromide or iodide, shaken well and precipitated with ether. *2-β-Anilinovinyl-6-methylpyridine metho-p-toluenesulphonate* crystallised from water and formed shining, flat, yellow needles with a pink reflex, m. p. 234° (Found : N, 7·05. $C_{22}H_{24}O_3N_2S$ requires N, 7·05%). *2-β-Acetanilidovinyl-6-methylpyridine methoperchlorate* crystallised from alcohol in large, flat, rectangular aggregates of needles, m. p. 210° (Found : N, 7·85; Cl, 9·9. $C_{17}H_{19}O_5N_2Cl$ requires N, 7·65; Cl, 9·7%). *2-β-Anilinovinyl-6-methylpyridine etho-p-toluenesulphonate monohydrate* crystallised from alcohol in flat orange needles, m. p. 148—150° (effervescence) (Found : N, 6·55. $C_{23}H_{26}O_3N_2S,H_2O$ requires N, 6·55%). *2-β-Anilinovinyl-4-methylpyridine methobromide* crystallised from *iso*propyl alcohol in clusters of yellow needles, m. p. 236° (Found : Br, 26·4. $C_{15}H_{17}N_2Br$ requires Br, 26·2%). *2-β-Anilinovinyl-4 : 6-dimethylpyridine metho-p-toluenesulphonate* formed bright orange feathery needles, m. p. 235°, from water (Found : N, 6·9. $C_{23}H_{26}O_3N_2S$ requires N, 6·8%). The *ethiodide dihydrate* formed flat orange needles, m. p. 265° (Found : I, 30·65. $C_{17}H_{21}N_2I,2H_2O$ requires I, 30·5%). The *anhydrous* salt, m. p. 265°, was obtained on heating the hydrate for 3 hours at 150°/20 mm. over potassium hydroxide (Found : I, 33·75. $C_{17}H_{21}N_2I$ requires I, 33·4%).

*2 : 6-Di-β-anilinovinylpyridine methochloride dihydrate* was obtained by refluxing at 200° in an oil bath, 2 : 6-dimethylpyridine metho-*p*-toluenesulphonate (1 mol.) and methyl*iso*formanilide (2 mol.) for 30 minutes. The melt was dissolved in hot alcohol and poured into an aqueous solution of ammonium chloride. The orange solid was well washed with cold alcohol, dissolved in hot alcohol and chilled in ice. The liquor set to a chrome-yellow gel. It formed matted yellow threads, m. p. 272°, with previous shrinking. It darkened appreciably in direct sunlight (Found : Cl, 8·85. $C_{23}H_{23}N_3Cl,2H_2O$ requires Cl, 8·85%). When dried over potassium hydroxide at 150°/20 mm., it gave the *anhydrous* salt, m. p. 272° (Found : Cl, 10·05. $C_{23}H_{23}N_3Cl$ requires Cl, 9·75).

*2 : 6-Di-β-acetanilidovinylpyridine methochloride* was precipitated on adding ether to the acetic anhydride solution of the above. Repeatedly dissolved in acetic anhydride and precipitated with ether it formed pale yellow needles, m. p. 106—108° (Found : Cl, 7·25. $C_{26}H_{26}O_3N_2Cl$ requires Cl, 7·9%).

*2 : 6-Di-β-anilinovinylpyridine ethochloride monohydrate.* Proceeding as for the methochloride this substance formed feathery bronze needles from alcohol, m. p. 240—245° (decomp.), with previous shrinking (Found : Cl, 8·8. $C_{23}H_{24}N_3Cl,H_2O$ requires Cl, 8·95%). When dried over potassium hydroxide at 150°/20 mm., it gave the *anhydrous* salt, m. p. 242—245° (Found : Cl, 9·05. $C_{23}H_{24}N_3Cl$ requires Cl, 9·4%).

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## 35. *The Kinetics of Anionotropic Rearrangement. Part III. Substituent Effects in the Oxotropic* Formation of the Vinylacetylene System.*

By ERNEST A. BRAUDE AND E. R. H. JONES.

Rate constants, energies of activation and solvent effects are reported for the acid-catalysed isomerisation of twenty carbinols of the type $CR_1R_2{:}CR_3{\cdot}CR_4(OH){\cdot}C{:}CR_5$. The rate constants at one temperature vary over a range of $10^9$, increasing with increasing alkyl substitution, and the isodielectric energies of activation, which are independent of solvent composition, vary from 20 to 32 kg.-cals. per mol. These results are explained by the mechanism proposed in Parts I and II (J., 1944, 436, 443) for the rearrangement of propenylethynylcarbinol ($R_1$ = Me; $R_2 = R_3 = R_4 = R_5$ = H), the establishment of the oxonium-ion equilibrium, $ROH \rightleftharpoons ROH_2^+$, being followed by the rate-determining isomerisation. A quantitative comparison is made of the general inductive and tautomeric effects of a number of alkyl and alkenyl groups.

IN Parts I and II (*loc. cit.*) a detailed kinetic study of the acid-catalysed rearrangement of propenylethynylcarbinol (IV) to hex-3-en-5-yn-2-ol was reported, the course of the reaction being followed by measuring the

(IV.) $CH_2{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH \xrightarrow{acid} CH_2{\cdot}CH(OH){\cdot}CH{=}CH{\cdot}C{\equiv}CH$

changing intensity of ultra-violet light absorption. The investigation has now been extended to 20 other carbinols of the same type, all of which have been prepared in the course of other studies carried out in these laboratories (Heilbron, Jones, *et al.*, J., 1942—1946) and a suitable opportunity has been provided for a quantitative comparison of the electronic effects of a number of alkyl and alkenyl groups in purely aliphatic systems.

As in the case of propenylethynylcarbinol (subsequently referred to as (IV) ), the reaction was always found to be of the first order and the first-order rate constant was independent of the carbinol concentration. Rate

* For the definition of Oxotropy, see Part I (J., 1944, 442).

constants, solvent effects, Arrhenius and isodielectric energies of activation are given in Table I. As far as possible, 0·002—1M-solutions of hydrochloric acid in 60 and 80% (by volume) alcohol were used as reaction media and, for convenience, a carbinol concentration of 0·700% w/v was employed throughout, except in the case of the sparingly soluble glycol (XX) where $c_{ROH}$ was 0·14%. The 60 and 80% alcohol–water mixtures were chosen since most of the carbinols studied are insufficiently soluble when $c_{EtOH} < 60\%$, and for $c_{EtOH} > 80\%$ the relation between dielectric constant ($D$) of the medium and log $k$ is no longer linear (Part II, *loc. cit.*) and

TABLE I.

$c_A$ = Concentration of HCl (mols./l.); $c_{EtOH}$ = vol.-% EtOH; $k$ = first-order rate constant (in min.$^{-1}$); carbinol concentration $c_{ROH}$ = 0·700% w/v throughout, except with (XX), where $c_{ROH}$ = 0·140%; $E_{60}$, $E_{80}$ = Arrhenius energy of activation (in kg.-cals.) for $c_{EtOH}$ = 60, 80; $m = (\log k_{60} - \log k_{80})/(D_{60} - D_{80})$, where $D$ = dielectric constant (see Part II, *loc. cit.*); $E_{[D]60}$, $E_{[D]80}$ = isodielectric energies of activation (in kg.-cals.) for $c_{EtOH}$ = 60, 80.

| $t$. | $c_A$. | $c_{EtOH}$. | $10^4k$.* | |
|---|---|---|---|---|
| | (I) $CH_2{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH$. | | | |
| 30° | 4 | 20 | *0·8* | |
| | 4 | 40 | *0·4* | $E_{60}$ ~17 |
| | 4 | 60 | *0·3* | $E_{80}$ ~20 |
| 50 | 1 | 20 | *0·9* | $m$ = 0·033 |
| | 1 | 40 | *0·4* | $E_{[D]60}$ ~22 |
| 60 | 1 | 20 | *2* | $E_{[D]80}$ ~23 |
| | 1 | 40 | *1* | |
| | (II) $CH_2{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CH$. | | | |
| 30 | 1 | 60 | 2 | |
| | 1 | 80 | 0·5 | $E_{60}$ ~25 |
| 40 | 1 | 60 | 6 | $E_{80}$ ~29 |
| | 1 | 80 | 2 | $m$ = 0·045 |
| 50 | 0·1 | 60 | 1 | $E_{[D]60}$ ~31 |
| | 1 | 60 | 28 | $E_{[D]80}$ ~33 |
| | 1 | 80 | 10 | |
| | (III) $CH_2{=}CMe{\cdot}CH(OH){\cdot}C{\equiv}CH$. | | | |
| 30 | 4 | 60 | *2* | $E_{60}$ ~26 |
| 50 | 1 | 60 | *0·3* | $E_{80}$ ~28 |
| | 1 | 80 | *0·15* | $m$ = 0·036 |
| 60 | 1 | 60 | *1* | $E_{[D]60}$ ~31 |
| | 1 | 80 | *0·4* | $E_{[D]80}$ ~32 |
| | (IV) $CHMe{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH$. | | | |
| 30 | 0·02 | 60 | 0·078 | |
| | 0·1 | 60 | 0·58 | |
| | 0·1 | 80 | 0·210 | |
| | 1M-AcOH | 60 | 0·170 | |
| 40 | 0·02 | 60 | 0·366 | $E_{60}$ 25·7 |
| | 0·1 | 60 | 2·22 | $E_{80}$ 25·7 |
| | 0·1 | 80 | 0·85 | $m$ = 0·044 |
| 50 | 0·02 | 60 | 1·36 | $E_{[D]60}$ 31·4 |
| | 0·1 | 60 | 8·1 | $E_{[D]80}$ 30·7 |
| | 0·1 | 80 | 3·10 | |
| 60 | 0·02 | 60 | 3·98 | |
| | 0·1 | 60 | 28·1 | |
| | 0·1 | 80 | 10·0 | |
| | (V) $CHMe{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CH$. | | | |
| 30 | 0·02 | 60 | 17·5 | |
| | 0·1 | 60 | 93 | |
| | 0·1 | 80 | 30·7 | $E_{60}$ 23·7 |
| 40 | 0·02 | 60 | 56 | $E_{80}$ 25·7 |
| | 0·1 | 60 | 290 | $m$ = 0·040 |
| | 0·1 | 80 | 95 | $E_{[D]60}$ 28·8 |
| 50 | 0·02 | 60 | 210 | $E_{[D]80}$ 29·7 |
| | 0·1 | 60 | 1070 | |
| | 0·1 | 80 | 431 | |
| | (VI) $CHPr^n{=}CEt{\cdot}CH(OH){\cdot}C{\equiv}CH$. | | | |
| 30 | 0·04 | 60 | 1·17 | |
| | 0·1 | 60 | 2·80 | |
| | 0·1 | 80 | 1·25 | $E_{60}$ 27·2 |
| 40 | 0·04 | 60 | 4·84 | $E_{80}$ 27·7 |
| | 0·1 | 60 | 13·5 | $m$ = 0·031 |
| | 0·1 | 80 | 6·0 | $E_{[D]60}$ 31·2 |
| 50 | 0·04 | 60 | 18·0 | $E_{[D]80}$ 30·8 |
| | 0·1 | 60 | 46·7 | |
| | 0·1 | 80 | 21·9 | |

| $t$. | $c_A$. | $c_{EtOH}$. | $10^4k$.* | |
|---|---|---|---|---|
| | (VII) $CMe_2{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH$. | | | |
| 30° | 0·02 | 60 | 27·3 | |
| | 0·02 | 80 | 6·9 | $E_{60}$ 21·7 |
| | 0·1 | 60 | 133 | $E_{80}$ 23·2 |
| 40 | 0·02 | 60 | 85 | $m$ = 0·046 |
| | 0·02 | 80 | 26·4 | $E_{[D]60}$ 27·6 |
| 50 | 0·02 | 60 | 256 | $E_{[D]80}$ 27·6 |
| | 0·02 | 80 | 81 | |
| | (VIII) $CMe_2{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CH$. | | | |
| 30 | 0·002 | 60 | 70 | |
| | 0·02 | 60 | 820 | |
| | 0·02 | 80 | 337 | $E_{60}$ 21·4 |
| 40 | 0·002 | 60 | 221 | $E_{80}$ 21·6 |
| | 0·002 | 80 | 98 | $m$ = 0·030 |
| | 0·02 | 60 | 2530 | $E_{[D]60}$ 25·2 |
| 50 | 0·002 | 60 | 640 | $E_{[D]80}$ 24·6 |
| | 0·02 | 60 | 7000 | |
| | 0·02 | 80 | 3620 | |
| | (IX) $CH_2{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CBu$ ($n$). | | | |
| 30 | 1 | 60 | 1·4 | |
| | 1 | 80 | 0·5 | $E_{60}$ ~18·5 |
| 40 | 1 | 60 | 4·7 | $E_{80}$ ~19·5 |
| | 1 | 80 | 1·8 | $m$ = 0·038 |
| 50 | 0·1 | 60 | 0·56 | $E_{[D]60}$ ~23·5 |
| | 1 | 60 | 9·4 | $E_{[D]80}$ ~23 |
| | 1 | 80 | 2·8 | |
| | (X) $CH_2{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CBu$ ($n$). | | | |
| 30 | 0·02 | 60 | 2·90 | |
| | 0·1 | 60 | 16·4 | $E_{60}$ 26·0 |
| | 0·1 | 80 | 5·0 | $E_{80}$ 27·6 |
| 40 | 0·1 | 60 | 68 | $m$ = 0·043 |
| | 0·1 | 80 | 21·1 | $E_{[D]60}$ 31·5 |
| 50 | 0·1 | 60 | 244 | $E_{[D]80}$ 31·9 |
| | 0·1 | 80 | 86 | |
| | (XI) $CHMe{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CBu$ ($n$). | | | |
| 0 | 0·1 | 60 | 1·49 | |
| 30 | 0·02 | 60 | 16·5 | |
| | 0·1 | 60 | 81 | |
| | 0·1 | 80 | 32·0 | |
| | 1 | 60 | 1760 | $E_{60}$ 22·2 |
| | 1M-AcOH | 60 | 0·84 | $E_{80}$ 23·7 |
| 40 | 0·02 | 60 | 44·7 | $m$ = 0·030 |
| | 0·1 | 60 | 219 | $E_{[D]60}$ 26·0 |
| | 0·1 | 80 | 105 | $E_{[D]80}$ 26·7 |
| 50 | 0·02 | 60 | 162 | |
| | 0·1 | 60 | 800 | |
| | 0·1 | 80 | 395 | |
| | (XII) $CHMe{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CBu$ ($n$) | | | |
| 30 | 0·0004 | 90 | 1·26 | |
| | 0·002 | 60 | 111 | |
| | 0·002 | 80 | 32·6 | $E_{60}$ 22·8 |
| | 0·02 | 60 | 1040 | $E_{80}$ 23·2 |
| 40 | 0·002 | 60 | 352 | $m$ = 0·042 |
| | 0·002 | 80 | 141 | $E_{[D]60}$ 28·1 |
| 50 | 0·0004 | 90 | 12·8 | $E_{[D]80}$ 27·4 |
| | 0·002 | 60 | 1160 | |
| | 0·002 | 80 | 363 | |

| *t.* | $c_A$. | $c_{EtOH}$. | $10^4k$.* | |
|---|---|---|---|---|
| | (XIII) $CMe_2$=CH·CMe(OH)·C≡CBu (*n*). | | | |
| 30° | 0·0004 | 90 | 98 | $E_{60}$ 20 ~25 |
| | 0·002 | 90 | 1700 | |
| 40 | 0·0004 | 90 | 206 | |
| 50 | 0·0004 | 90 | 820 | |
| | (XIV) CHMe=CH·CH(OH)·C≡C·$CH_2$OMe. | | | |
| 30 | 0·1 | 60 | 2·30 | $E_{60}$ 27·5 |
| | 0·1 | 80 | 0·90 | $m$ = 0·035 |
| | 0·2 | 60 | 5·8 | $E_{[D]60}$ 32·0 |
| | 1 | 60 | 90 | |
| 40 | 0·1 | 60 | 9·3 | |
| 50 | 0·1 | 60 | 39·4 | |
| | (XV) CHMe=CH·CMe(OH)·C≡C·$CH_2$OMe. | | | |
| 30 | 0·02 | 60 | 63 | $E_{60}$26·1 |
| | 0·02 | 80 | 25·5 | $m$ = 0·033 |
| | 0·1 | 60 | 355 | $E_{[D,60}$ 30·2 |
| 40 | 0·02 | 60 | 288 | |
| 50 | 0·02 | 60 | *930* | |
| | (XVI) $CMe_2$=CH·CMe(OH)·C≡C·$CH_2$OMe. | | | |
| 30 | 0·002 | 60 | 201 | $E_{60}$ 19·2 |
| | 0·002 | 80 | 84 | $m$ = 0·032 |
| | 0·02 | 60 | 2040 | $E_{[D]60}$ 23·3 |
| 40 | 0·002 | 60 | 560 | |
| 50 | 0·002 | 60 | 1470 | |
| | (XVII) CHMe=CH·CH(OH)·C≡C·CH=$CH_2$. | | | |
| 30 | 0·02 | 60 | 5·9 | $E_{60}$ 22·4 |
| | 0·1 | 60 | 34·8 | $E_{80}$ 24·1 |
| | 0·1 | 80 | 12·4 | $m$ = 0·036 |
| 40 | 0·02 | 60 | 21·3 | $E_{[D]60}$ 27·0 |
| | 0·1 | 60 | 113 | $E_{[D]80}$ 27·7 |
| | 0·1 | 80 | 43·2 | |
| 50 | 0·02 | 60 | 68 | |
| | 0·1 | 60 | 352 | |
| | 0·1 | 80 | 150 | |

| *t.* | $c_A$. | $c_{EtOH}$. | $10^4k$.* | |
|---|---|---|---|---|
| | (XVIII) CHMe=CH·CH(OH)·C≡C·CMe=$CH_2$. | | | |
| 30° | 0·02 | 60 | 7·9 | $E_{60}$ 20·9 |
| | 0·1 | 60 | 42·6 | $E_{80}$ 22·9 |
| | 0·1 | 80 | 15·7 | $m$ = 0·034 |
| 40 | 0·02 | 60 | 22·1 | $E_{[D]60}$ 25·2 |
| | 0·1 | 60 | 123 | $E_{[D]80}$ 26·3 |
| | 0·1 | 80 | 51 | |
| 50 | 0·02 | 60 | 79 | |
| | 0·1 | 60 | 370 | |
| | 0·1 | 80 | 167 | |
| | (XIX) CHMe=CH·CH(OH)·C≡C·CMe=CHMe. | | | |
| 30 | 0·04 | 60 | 47·8 | $E_{60}$ 22·5 |
| | 0·1 | 60 | 116 | $m$ = 0·025 |
| | 0·1 | 80 | 65·0 | $E_{[D]60}$ 25·7 |
| 40 | 0·1 | 60 | 368 | |
| 50 | 0·1 | 60 | 1200 | |
| | (XX) CHMe=CH·CH(OH)·C≡C·CH(OH)·CH=CHMe. | | | |
| 30 | 0·04 | 60 | 2·50 | $E_{60}$ 25·4 |
| | 0·1 | 60 | 7·3 | $E_{80}$ 26·9 |
| | 0·1 | 80 | 2·94 | $m$ = 0·032 |
| 40 | 0·04 | 60 | 9·2 | $E_{[D]60}$ 29·5 |
| | 0·1 | 60 | 29·2 | $E_{[D]80}$ 30·1 |
| | 0·1 | 80 | 11·4 | |
| 50 | 0·04 | 60 | 39·5 | |
| | 0·1 | 60 | 96 | |
| | 0·1 | 80 | 47·6 | |

* Values extrapolated to zero time in italics.

does not permit of the evaluation of isodielectric energies of activation. In three cases, however, other media had to be used. At room temperature, the rates of rearrangement of (I) and (III) are so slow and the extent of polymerisation and decomposition so great that 4M-hydrochloric acid had to be used as catalyst to attain measurable rates, although considerable chloro-compound formation takes place at such high acid concentrations. Solutions of carbinol (XIII) could only be obtained in 90% alcohol, a comparison of the relative rate constant being obtained by carrying out the rearrangement of (XII) in this medium also.

The rate constants are roughly proportional to the acid concentration ($c_A$) up to $c_A$ = 0·1M [for the rearrangement of (IV) in 20% alcohol (Part I, *loc. cit.*) this proportionality was strict]; in 60% and 80% alcohol the rate constants generally increase slightly more rapidly than $c_A$, but the increase in the " catalytic constant " ($k/c_A$) in no case exceeds 20% for a ten-fold increase in $c_A$. The degree of deviation from linearity of the $k$–$c_A$ curve varies for different carbinols; it is definitely greater than the maximum experimental error in several cases and the differences are probably to be ascribed to solvation effects. If the deviations were solely due to the fact that the catalytic effect of the medium at high alcohol concentrations is no longer proportional to $c_A$ even for $c_A$ < 0·1M, the differences should be the same for all carbinols. In 90% alcohol the proportionality between $k$ and $c_A$ is completely destroyed, as shown by the values of $k$ for (XIII).

Above $c_A$ = 0·1, $k$ increases more rapidly than $c_A$ as in the case of (IV), where $k$ is proportional to Hammett's acidity function $H_0$ (Part I, *loc. cit.*). Again, the ratio of the rate constants of the rearrangement of (XI) in hydrochloric and acetic acid is nearly the same as in the case of (IV).

The solvent effect varies somewhat for different carbinols, the rate constants decreasing by factors ranging from 2 to 4 when $c_{EtOH}$ is increased from 60 to 80%. Arrhenius energies of activation range from 19 to 27 kg.-cals./mol., and the values for 60 and 80% alcohol respectively show a maximum difference of ±1 kg.-cal. and an average difference of ±0·6 kg.-cal. Isodielectric energies of activation, calculated from the solvent-effect data by the method previously described (Part II, *loc. cit.*), are also given in Table I. They range from 18·5 to 31·5 kg.-cals./mol., but differences between the values for 60 and 80% alcohol are reduced to a maximum of ±0·5 kg.-cal. and an average of ±0·3 kg.-cal. The accuracy of the rate constants and hence of the energies of activation varies considerably for different carbinols (see Experimental), but since the average probable error in $E$ is estimated at ±0·3 kg.-cal./mol., isodielectric energies of activation are therefore independent of medium composition within the limits of experimental error, as has already been observed in the case of propenylethynylcarbinol (IV) (Part II, *loc. cit.*).*

* The isodielectric energy of activation ($E_{[D]}$) is the energy of activation when $D$ is constant *at different temperatures* for *one* solvent, *i.e.*, for a solvent of temperature-invariant dielectric constant, but different solvents of different dielectric constants may of course give rise to different values of $E_{[D]}$.

## Experimental.

The technique of the kinetic measurements has been described in Part I, but owing to the fact that the more unstable carbinols studied often showed appreciable initial light absorption, a slightly different method of computation was employed. The first-order rate constant $k$ was calculated from $k = (2{\cdot}3/z) \log [(a - x_0)/(a - x)]$ where $z$ = time in minutes, $x_0$ = intensity of absorption at $z = 0$, $x$ = intensity at $z$ mins., $a$ = intensity at $z = \infty$, intensities being expressed as $E^{1\%}_{1\text{cm.}}$ at the wave-length of the maximum. In order to reduce incidental errors to a minimum, $x_0$ was determined directly from the carbinol, not from the reaction mixture, and was repeatedly checked since it often increased slowly on standing during several weeks, even at 0°. The range of $x_0$ values is shown in Table II. Initial absorption is particularly marked in the tertiary carbinols, possibly owing to slow dehydration, and in the propargylcarbinols. No definite case of thermal isomerisation has been observed, and the initial absorption could usually be eliminated by refractionation, but in general it was impracticable to use freshly distilled samples for every run owing to lack of material.

The end-values $a$ were again averaged from all the end-values obtained in individual runs; the absorption intensities so obtained are in most cases close to those reported in the preparative work (Heilbron, Jones, *et al.*, *loc. cit.*) where the carbinols were rearranged heterogeneously and the pure products isolated (Table II). In some cases the kinetic end-values are slightly higher, suggesting that the heterogeneous rearrangements were not quite complete; in others they are somewhat lower, suggesting that side reactions occur in the homogeneous media leading to less strongly absorbing products. The third alternative, namely, that an equilibrium is set up between the unrearranged and the rearranged isomers, can be discounted because end-values were the same at different temperatures; if an equilibrium did occur, the equilibrium constant, and, therefore, the final absorption intensity would, of course, vary with temperature. The isomerisations of the four vinylcarbinols (I), (II), (III), and (IX) are so slow, and decomposition so rapid, that it is impossible to follow the reactions to completion. The highest extinction coefficients attained correspond to 10, 80, 10 and 90% rearrangement respectively. Except in the case of (II) the previous attempts to effect these rearrangements heterogeneously had failed completely. The rearranged isomer of (I) has, however, been prepared *via* the corresponding chloro-compound, and the intensity there obtained was used for $a$; end-values for (III) and (IX), the isomers of which have not been isolated, were deduced by assuming $\varepsilon_{max.} (= E^{1\%}_{1\text{cm.}} \times M/10) = 13000$ for the fully rearranged carbinol, this being the average value in this series; but with (I) and (III), no conclusive evidence has been obtained as to whether *complete* rearrangement does in fact occur or not.

Table II.

| Rearrangement of carbinol. | $\lambda_{max.}$, A. | $E^{1\%}_{1\text{cm.}}$ (max.), "kinetic." | "preparative." | $x_0$. | Accuracy of $k$'s. |
|---|---|---|---|---|---|
| (I) | 2230 | 1650 * | 1650 [7] | < 2 | δ |
| (II) | 2235 | 1300 * | 1300 [8] | 20 | γ |
| (III) | 2230 | 1300 * | — | < 2 | δ |
| (IV) | 2235 | 1300 | 1300 [1] | < 2 | α |
| (V) | 2240 | 1130 | 1200 [8] | 35 | α |
| (VI) | 2270 | 815 | 820 [1] | 35—45 | β |
| (VII) | 2235 | 1140 | 1180 [1] | 25 | β |
| VIII) | 2240 | 965 | 960 [8] | 50 | α |
| (IX) | 2280 | 1000 * | — | 65—140 | γ |
| (X) | 2280 | 870 | 920 [6] | 80 | β |
| (XI) | 2280 | 1100 | 1060 [2] | < 2 | α |
| (XII) | 2280 | 920 | 870 [6] | 20 | α |
| (XIII) | 2280 | 575 | 680 [6] | 100 | β |
| (XIV) | 2280 | 940 | 910 [9] | 180 | α |
| (XV) | 2280 | 800 | 770 [9] | 70—80 | β |
| (XVI) | 2280 | 600 | 760 [9] | 65—105 | β |
| (XVII) | 2585 | 1400 | 1450 [5] | 10—20 | α |
| (XVIII) | 2590 | 1250 | 1260 [5] | 10—20 | α |
| (XIX) | 2620 | 1100 | 1100 [3] | 30—40 | α |
| (XX) | 2640 | 1290 | 1060 [4] | < 2 | α |

* Assumed.

[1] Jones and McCombie, J., 1943, 261. [2] Heilbron, Jones, and Raphael, J., 1943, 264. [3] Heilbron, Johnson, Jones, and Raphael, J., 1943, 265. [4] Heilbron, Jones, and Raphael, J., 1943, 268. [5] Heilbron, Jones, and Weedon, J., 1944, 140. [6] Cymerman, Heilbron, and Jones, J., 1944, 144. [7] Heilbron, Jones, Lacey, McCombie, and Raphael, J., 1945, 77. [8] Cymerman, Heilbron, and Jones, J., 1945, 90. [9] Heilbron, Jones, and Lacey, this vol., p. 27.

The instability of several of the carbinols studied has already been commented upon and severely limited the accuracy of the rate-constant determinations, the precaution of carrying out the rearrangements under nitrogen proving of little avail. Definite drifts in the rate constant were, however, only observed in isolated cases, and in these $k$ was extrapolated to zero time, as indicated in Table I. The average maximum errors in the rate constants for each carbinol are indicated in Table II, where α denotes an accuracy in $k$ of about ±2%, β of ±5% and γ of ±10%, whereas δ denotes that the maximum error is uncertain and may considerably exceed 10%. Some 30% of the rate constant determinations were carried out in duplicate. Four individual runs, exemplifying the four grades of accuracy attained, are reproduced below. The carbinol concentration was 0·7% w/v throughout.

Rearrangement of (V) in 0·1M-HCl, 80% by vol. EtOH, 30°.

| Time (mins.). | $E^{1\%}_{1\text{cm.}}$ at 2240 A. | $10^4k$ (min.$^{-1}$). | Time (mins.). | $E^{1\%}_{1\text{cm.}}$ at 2240 A. | $10^4k$ (min.$^{-1}$). |
|---|---|---|---|---|---|
| 0 | 36 | — | 367 | 785 | 30·6 |
| 163 | 465 | 30·5 | ∞ | 1130 | — |
| 272 | 658 | 30·9 | | | Mean 30·7 (± <2%) |

Rearrangement of (VII) in 0·02M-HCl, 60% by vol. EtOH, 50°.

| Time (mins.). | $E^{1\%}_{1\text{cm.}}$ at 2235 A. | $10^4k$ (min.$^{-1}$). | Time (mins.). | $E^{1\%}_{1\text{cm.}}$ at 2235 A. | $10^4k$ (min.$^{-1}$). |
|---|---|---|---|---|---|
| 0 | 25 | — | 36 | 704 | 260 |
| 12 | 328 | 262 | ∞ | 1140 | — |
| 22 | 493 | 248 | | | Mean 256 (± <5%) |
| 29 | 610 | 255 | | | |

Rearrangement of (IX) in 1M-HCl, 60% by vol. EtOH, 30°.

| Time (mins.). | $E^{1\%}_{1\,cm.}$ at 2280 A. | $10^4k$ (min.$^{-1}$). | Time (mins.). | $E^{1\%}_{1\,cm.}$ at 2280 A. | $10^4k$ (min.$^{-1}$). |
|---|---|---|---|---|---|
| 0 | 65 | — | 7595 | 680 | 1·41 |
| 1410 | 243 | 1·50 | ∞ | 1000 * | — |
| 2590 | 336 | 1·32 | | | Mean 1·40 (±<10%) |
| 4610 | 500 | 1·35 | | | |

Rearrangement of (I) in 4M-HCl, 60% by vol. EtOH, 30°.

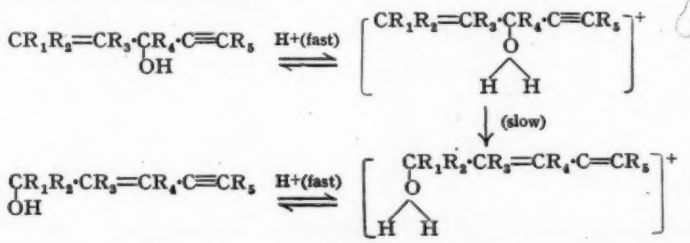
| Time (mins.). | $E^{1\%}_{1\,cm.}$ at 2230 A. | $10^4k$ (min.$^{-1}$). | Time (mins.). | $E^{1\%}_{1\,cm.}$ at 2230 A. | $10^4k$ (min.$^{-1}$). |
|---|---|---|---|---|---|
| 0 | 0 | 0·30 † | 8,550 | 324 | 0·256 |
| 1540 | 72 | 0·292 | 11,200 | 395 | 0·230 |
| 2860 | 127 | 0·281 | ∞ | 1650 * | — |
| 5800 | 256 | 0·290 | | | |

* Assumed. † Extrapolated.

Arrhenius energies of activation were calculated algebraically from $E = 2{\cdot}3\,\boldsymbol{R} \log (k_2/k_1) \times T_1T_2/(T_2 - T_1)$. The deviation from the mean of individual values of $E$ varied from ±0·1 to ±2 kg.-cal./mol., the magnitude of the deviations being roughly proportional to the estimated probable errors in the rate-constant determinations. Isodielectric energies of activation were calculated by $E_{[D]} = E_{Arr.} + 2{\cdot}3\boldsymbol{R}T_1T_2mb$, where $b = 0{\cdot}286$ and 0·225 respectively for $c_{EtOH} = 60\%$ and $c_{EtOH} = 80\%$ (see Part II, *loc. cit.*). Values of $m$ are averaged over the temperature range employed.

## Discussion.

Since such characteristics of the isomerisation as reaction order, dependence of rate constants on carbinol, acid and alcohol concentrations, etc., are identical in every case with those found for the rearrangement of propenylethynylcarbinol (IV), it would appear that the mechanism throughout the series is that previously proposed for the isomerisation of the latter compound, *viz.*,



according to which a reversible oxonium-ion formation is followed by the rate-determining isomerisation, the driving force of which must consist essentially of the tendency of the double to become conjugated with the acetylenic linkage. Both steps of the reaction should be facilitated by an increased electron availability at the oxygen atom. Inspection of the rate constants of the rearrangement for the various carbinols under identical conditions (Table III) shows that this is indeed the case, the rate constants increasing rapidly with increasing substitution by (electron-repelling) alkyl groups, over a range of $10^9$. An alkyl substituent on carbon atom 2 in the system $\overset{1}{C}{=}\overset{2}{C}{-}\overset{3}{C}(OH){-}\overset{4}{C}{\equiv}\overset{5}{C}$ has a much smaller effect, however, than a similar substituent

## Table III.

$r$ = Observed rate constant at 30° in 60% EtOH relative to that of carbinol (IV). $r_{calc.}$ = Relative rate constant calculated by (1).

| Carbinol. | $10^4k$ (min.$^{-1}$) in 0·1M-HCl, 60% EtOH, 30°.* | $E_{[D]}$ in 60% EtOH. | log $A$. | $r$. | log $r$. | log $r_{calc.}$ | log $r_{calc.}$ − log $r$. |
|---|---|---|---|---|---|---|---|
| (I) $CH_2{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH$ | *0·00015* | ~22 | ~6 | 0·0003 | −3·5 | −3·5 | 0·0 |
| (II) $CH_2{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CH$ | *0·09* | ~31 | ~15 | 0·15 | −0·8 | −1·1 | −0·3 |
| (III) $CH_2{=}CMe{\cdot}CH(OH){\cdot}C{\equiv}CH$ | *0·0011* | ~31 | ~13 | 0·002 | −2·7 | −2·7 | 0·0 |
| (IV) $CHMe{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH$ | 0·58 | 31·4 | 16·6 | 1 | 0 | 0·0 | 0·0 |
| (V) $CHMe{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CH$ | 93 | 28·8 | 17·0 | 160 | 2·2 | 2·4 | +0·2 |
| (VI) $CHPr^{\alpha}{=}CEt{\cdot}CH(OH){\cdot}C{\equiv}CH$ | 2·80 | 31·2 | 17·2 | 5 | 0·7 | 0·8 | +0·1 |
| (VII) $CMe_2{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH$ | 133 | 27·6 | 16·2 | 250 | 2·4 | 1·9 | −0·5 |
| (VIII) $CMe_2{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CH$ | *4,550* | 25·2 | 16·1 | 9,000 | 4·0 | 4·3 | +0·3 |
| (IX) $CH_2{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CBu(n)$ | *0·054* | ~23·5 | ~10 | 0·1 | −1·0 | −1·4 | −0·4 |
| (X) $CH_2{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CBu(n)$ | 16·4 | 31·5 | 18·1 | 30 | 1·5 | 1·0 | −0·5 |
| (XI) $CHMe{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CBu(n)$ | 81 | 26·0 | 14·9 | 150 | 2·2 | 2·1 | −0·1 |
| (XII) $CHMe{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CBu(n)$ | *5,600* | 28·2 | 18·3 | 11,000 | 4·0 | 4·5 | +0·5 |
| (XIII) $CMe_2{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CBu(n)$ | *354,000* | ~25 | ~18 | 700,000 | 5·9 | 6·4 | +0·5 |
| (XIV) $CHMe{=}CH{\cdot}CH(OH){\cdot}C{\equiv}C{\cdot}CH_2OMe$ | 2·30 | 32·0 | 17·7 | 4 | 0·6 | 0·5 | −0·1 |
| (XV) $CHMe{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}C{\cdot}CH_2OMe$ | 355 | 30·2 | 18·6 | 600 | 2·8 | 2· | −0·2 |
| (XVI) $CMe_2{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}C{\cdot}CH_2OMe$ | *10,200* | 23·3 | 15·1 | 2,000 | 4·3 | 4·5 | +0·2 |
| (XVII) $CHMe{=}CH{\cdot}CH(OH){\cdot}C{\equiv}C{\cdot}CH{=}CH_2$ | 34·8 | 27·0 | 15·2 | 60 | 1·8 | 1·8 | 0·0 |
| (XVIII) $CHMe{=}CH{\cdot}CH(OH){\cdot}C{\equiv}C{\cdot}CMe{=}CH_2$ | 42·6 | 25·2 | 14·0 | 25 | 1·9 | 1·9 | 0·0 |
| (XIX) $CHMe{=}CH{\cdot}CH(OH){\cdot}C{\equiv}C{\cdot}CMe{=}CHMe$ | 116 | 25·7 | 15·3 | 200 | 2·3 | 2·3 | 0·0 |
| (XX) $CHMe{=}CH{\cdot}CH(OH){\cdot}C{\equiv}C{\cdot}CH(OH){\cdot}CH{=}CHMe$ | 7·3 | 29·5 | 16·4 | | 1·1 | — | — |

* Extrapolated values in italics.

on carbon atoms 1, 3, or 5. An alkenyl group on carbon atom 5 has an effect similar in magnitude to that of an alkyl group, while an alkoxymethyl group has a smaller influence on the rate constant.

In Table III columns from left to right represent (i) the carbinol, (ii) the rate constant in, or extrapolated to, 0·1M-hydrochloric acid in 60% (by vol.) alcohol at 30° (extrapolated values in italics), (iii) the isodielectric energy of activation ($E_{[D]}$) in 60% (by vol.) alcohol [estimated in the cases of (I) and (XIII) where the media actually employed were 20% and 90% alcohol respectively, and also in the cases of (II), (III), and (IX) where the logarithms of the rate constants do not vary linearly with $1/T$, probably because the rate of decomposition is greatly increased at higher temperatures], (iv) log $A$, where $k = Ae^{-E_{[D]}/RT}$, (v) $r$, the relative rate constant with respect to (IV) which was chosen as reference compound rather than (I), because it has been most thoroughly investigated and its data are the most accurate available, (vi) log $r$, (vii) log $r$ calculated by equation (1) (see below).

The relative rate constants ($r$) vary over a range of $10^9$, while $E_{[D]}$ varies from 18·5 to 31·5 kg.-cals./mol. and log $A$ from 6·3 to 18·3. Variations in $r$ are therefore due to simultaneous variations in both $E_{[D]}$ and $A$. There is no obvious correlation between the degree of substitution and either $E_{[D]}$ or log $A$ separately, but the effect of a substituent on log $r$ is reasonably constant, and the relative rate constants at one temperature can be expressed by the equation

$$\log r = \log r_0 + \Sigma\Delta \log r \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $r_0$ refers to the unsubstituted compound (I) and $\Delta \log r$ represents the effect of each substituent present. The following values of $\Delta \log r$ lead to the smallest average difference ($\pm 0{\cdot}2$) between log $r_{calc.}$ and log $r_{obs.}$ (log $r_0 = -3{\cdot}5$) :

*Substituent effects in the rearrangement of* $\overset{1}{C}R_1R_2{=}\overset{2}{C}R_3{\cdot}\overset{3}{C}R_4(OH){\cdot}\overset{4}{C}{\equiv}\overset{5}{C}R_5$.

| Substituent. | Δ log *r*. | Substituent. | Δ log *r*. | Substituent. | Δ log *r*. |
|---|---|---|---|---|---|
| $R_1$ = Me or *n*-Pr ..... | 3·5 | $R_4$ = Me ..... | 2·4 | $R_5$ = CH=$CH_2$ ..... | 1·8 |
| $R_2$ = Me (when $R_1$ = Me) | 1·9 | $R_5$ = *n*-Bu ..... | 2·1 | $R_5$ = CMe=$CH_2$ ..... | 1·9 |
| $R_3$ = Me or Et ..... | 0·8 | $R_5$ = $CH_2$·OMe ..... | 0·5 | $R_5$ = CMe=CHMe ..... | 2·3 |

These results demonstrate very forcibly the operation of two types of substituent effect, one (general inductive) decreasing rapidly with distance between the substituent and the reacting centre, and the other (tautomeric) effective only when an unsaturated, highly polarisable group, *e.g.*, an ethylenic bond, is interposed between the substituent and the reacting centre (Ingold, J., 1933, 1120). In the present instance, the inductive effect would be expected to be fully exerted by a substituent on carbon atom 3. Introduction of a methyl group in this position ($R_4$ = Me) increases the rate constant by an average factor of 250. When a methyl group is attached to carbon atom 2 ($R_3$ = Me), further away from the hydroxyl group, the rate constant only increases by a factor of about 5. A methyl substituent on carbon atom 1, however, again has a very large effect (a factor of *ca.* 2500), in spite of the fact that the distance between the substituent and the reacting centre has been increased still further. The effect of the methyl group in this position must be ascribed almost entirely to its tautomeric effect. A second methyl substituent on carbon atom 1 has a less powerful action than the first, presumably because the polarisability of the ethylenic bond decreases with its increasing polarisation. It may be noted that an alkyl substituent on carbon atom 2 ($R_3$ = Me or Et) exerts only its positive inductive effect, and not, as might be expected, a simultaneous negative tautomeric effect by causing a displacement of the double bond electrons away from the reacting centre. The tautomeric properties of the alkyl groups in the present reaction must therefore be mainly time-variable polarisability (electromeric) effects, coming into play only if they facilitate the reaction and at the demand of the attacking hydrogen ion (cf. Shoppee, J., 1930, 968).

A *n*-butyl group attached to carbon atom 5 increases the rate constant by an average factor of 100, *i.e.*, very much less than a methyl group on carbon atom 1. This may be due both to a smaller polarisability of the acetylenic as compared with the ethylenic bond, and to a smaller tautomeric effect of the *n*-butyl as compared with the methyl group (cf. Baker and Nathan, J., 1935, 184; Baker, J., 1939, 1150). The tautomeric effect of the methoxymethyl group ($R_5$ = $CH_2$·OMe) is much smaller than that of an alkyl group, as would be expected. A *conjugated* vinyl group ($R_5$ = CH=$CH_2$) has quite a large electron-donating tautomeric effect, although the ethylenic double bond is normally an electron acceptor, because, when in conjugation, the mobility of all the unsaturation electrons in the conjugated system is increased. This effect is further enhanced by methyl substituents ($R_5$ = CMe=$CH_2$ and CMe=CHMe).

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## 36. *The Kinetics of Anionotropic Rearrangement. Part IV. Substituent Effects in the Oxotropic Formation of the Butadiene System. A Comparison of the Electron-attracting Properties of the Ethylenic and Acetylenic Bonds.*

By Ernest A. Braude and E. R. H. Jones.

First-order rate constants, energies of activation and solvent effects have been determined for the acid-catalysed isomerisation of four vinylcarbinols of the type $CR_1R_2{:}CR_3{\cdot}CR_4(OH){\cdot}CH{:}CH_2$. The results are discussed in relation to the data already reported in Part III (preceding paper) for the corresponding ethynylcarbinols. The reaction mechanism is the same in both series and the effect of methyl substituents is similar, but the vinylcarbinols have rate constants greater, by factors of 200 to 10,000, than those of the ethynylcarbinols, due to the smaller electron deficiency (negative inductive effect) of the ethylenic as compared with the acetylenic carbon atom adjacent to the carbinol group.

In Part III (*loc. cit.*) a detailed study was presented of substituent effects in the rearrangement of acetylenylcarbinols derived from αβ-unsaturated carbonyl compounds to the corresponding vinylacetylenic alcohols. The analogous oxotropic formation of the butadiene system by the rearrangement

$$CR_1R_2 = CR_3{\cdot}CR_4(OH){\cdot}CH = CH_2 \xrightarrow{\text{acids}} CR_1R_2(OH){\cdot}CR_3 = CR_4{\cdot}CH = CH_2$$

has now been examined, but the number of compounds studied has, for the time being, had to be restricted to four. Sufficient data have been accumulated, however, to show that the effect of methyl substituents is very similar in the two series and to obtain a measure of the relative magnitudes of the electron-attracting effects of the ethylenic and acetylenic bonds.

First-order rate constants, solvent effects, Arrhenius and isodielectric energies of activation (*i.e.*, energies of activation for media of temperature-invariant dielectric constant, calculated according to the method outlined in Part II, J., 1944, 443) are given in Table I. As in the case of the acetylenylcarbinols, the reaction is strictly

Table I.

$c_A$ = Concentration of HCl (mols./l.); $c_{EtOH}$ = vol.-% EtOH; $k$ = first-order rate constant; carbinol concentration ($c_{ROH}$) = 0·700% w/v throughout for (I) and (III), 0·350% w/v throughout for (II) and (IV); $E_{60}$, $E_{80}$ = Arrhenius energy of activation for $c_{EtOH}$ = 60, 80; $m$ = (log $k_{60}$ − log $k_{80}$)/($D_{60} - D_{80}$), where $D$ = dielectric constant (see Part II, *loc. cit.*); $E_{[D]60}$, $E_{[D]80}$ = isodielectric energies of activation for $c_{EtOH}$ = 60, 80.

| *t.* | $c_A$. | $c_{EtOH}$. | $10^4k$ (min.$^{-1}$). | |
|---|---|---|---|---|
| | (I) $CH_2{=}CH{\cdot}CH(OH){\cdot}CH{=}CH_2$. | | | |
| 30° | 0·02 | 60 | 0·340 | $E_{60}$ 24·3<br>$E_{80}$ 26·9<br>$m$ = 0·043<br>$E_{[D]60}$ 29·6<br>$E_{[D]80}$ 31·2 |
| | 0·1 | 60 | 1·80 | |
| | 0·1 | 80 | 0·50 | |
| | 0·4 | 60 | 10·4 | |
| | 1·0 | 60 | 37·7 | |
| 40 | 0·02 | 60 | 1·12 | |
| | 0·1 | 60 | 5·7 | |
| | 0·1 | 80 | 2·05 | |
| 50 | 0·02 | 60 | 4·13 | |
| | 0·1 | 60 | 22·2 | |
| | 0·1 | 80 | 8·0 | |
| 60 | 0·02 | 60 | 14·3 | |
| | (II) $CH_2{=}CMe{\cdot}CH(OH){\cdot}CH{=}CH_2$ | | | |
| 30 | 0·02 | 60 | 0·54 | $E_{60}$ 21·7<br>$E_{80}$ 26·6<br>$m$ = 0·049<br>$E_{[D]60}$ 27·9<br>$E_{[D]80}$ 31·0 |
| | 0·1 | 60 | 3·28 | |
| | 0·1 | 80 | 0·74 | |
| 40 | 0·02 | 60 | 2·28 | |
| | 0·1 | 60 | 11·4 | |
| | 0·1 | 80 | 3·15 | |
| 50 | 0·02 | 60 | 6·9 | |
| | 0·1 | 60 | 34·1 | |
| | 0·1 | 80 | 10·6 | |

| *t.* | $c_A$. | $c_{EtOH}$. | $10^4k$ (min.$^{-1}$). | |
|---|---|---|---|---|
| | (III) $CHMe{=}CH{\cdot}CH(OH){\cdot}CH{=}CH_2$ | | | |
| 0° | 0·005 | 60 | 2·36 | $E_{60}$ 20·1<br>$E_{80}$ 21·7<br>$m$ = 0·044<br>$E_{[D]60}$ 25·2<br>$E_{[D]80}$ 25·7 |
| 30 | 0·005 | 60 | 77 | |
| | 0·02 | 60 | 345 | |
| | 0·02 | 80 | 114 | |
| 40 | 0·005 | 60 | 235 | |
| | 0·02 | 60 | 1040 | |
| | 0·02 | 80 | 341 | |
| 50 | 0·005 | 60 | 690 | |
| | 0·02 | 60 | 2750 | |
| | 0·02 | 80 | 1080 | |
| | (IV) $CHMe{=}CH{\cdot}CMe(OH){\cdot}CH{=}CH_2$. | | | |
| 30 | 0·002 | 60 | 444 | $E_{60}$ 19·8<br>$E_{80}$ 21·4<br>$m$ = 0·044<br>$E_{[D]60}$ 25·4<br>$E_{[D]80}$ 25·8 |
| | 0·002 | 80 | 129 | |
| | 0·01 | 60 | 2200 | |
| 40 | 0·002 | 60 | 1340 | |
| | 0·002 | 80 | 415 | |
| 50 | 0·002 | 60 | 3410 | |
| | 0·002 | 80 | 1180 | |

of the first order and the first-order rate constants ($k$) are independent of the concentration of carbinol ($c_{ROH}$), nearly proportional to the acid concentration ($c_A$) below $c_A$ = 0·1, and decreased by factors of 2—4 on increasing the alcohol concentration from 60 to 80% by volume. Again, the ratio of the rate constants of (III) in 0·02M-

Table Ia.

Rearrangement of (III) in 1M-AcOH.

| *t.* | $c_{ROH}$, % w/v. | $c_{EtOH}$, % vol. | $10^4k$ (min.$^{-1}$). | |
|---|---|---|---|---|
| 30° | 0·700 | 40 | 100 | $E_{60}$ 19·0<br>$m$ = 0·075<br>$E_{[D]60}$ 28·0 |
| | 0·700 | 60 | 14·7 | |
| | 0·700 | 80 | 1·38 | |
| | 3·50 | 80 | 1·41 | |
| 40° | 0·700 | 60 | 38·6 | $E_{60}$ 19·0<br>$m$ = 0·075<br>$E_{[D]60}$ 28·0 |
| 50 | 0·700 | 60 | 105 | |

hydrochloric and 1M-acetic acid is practically the same as those found for propenylethynyl- and propenylhexynylcarbinols (Part I, Braude and Jones, J., 1944, 436; Parts II and III, *loc. cit.*), the values of $k_{0\cdot02M\text{-HCl}}/k_{1M\text{-AcOH}}$ in 60% EtOH being 23, 20 and 20 respectively; also the solvent effect is much larger for the weak acid.

## Experimental.

The preparation and properties of the carbinols studied have already been described (Heilbron, Jones, McCombie, and Weedon, J., 1945, 84; Cymerman, Heilbron, and Jones, J., 1945, 90), and the procedure employed in the kinetic measurements was identical with that described in Parts I and III (*loc. cit.*). The absorption intensities of the butadienylcarbinols are considerably higher than those of the vinylacetylenylcarbinols, with an average value of $\varepsilon_{max.} = 25{,}000$ at $\lambda_{max.} = 2230$ A. in the former as compared with $\varepsilon_{max.} = 13{,}000$ in the latter series. End values ($a$), initial values ($x_0$) and the estimated accuracies of the rate constants are given in Table II ($\alpha \pm 2\%$, $\beta \pm 5\%$, $\gamma \pm 10\%$).

### Table II.

| Carbinol. | $\lambda_{max.}$, A. | $a$, $E^{1\%}_{1cm.}$ (max.), "kinetic." | "preparative." | $x_0$. | Accuracy of $k$'s. |
|---|---|---|---|---|---|
| (I) | 2240 | 3000 * | 3000 [1] | <2 | $\gamma$ |
| (II) | 2280 | 2300 * | 2400 [1] | <2 | $\gamma$ |
| (III) | 2240 | 2550 | 2800 [1] | <2 | $\alpha$ |
| (IV) | 2280 | 1800 | 2100 [2] | 35 | $\beta$ |

* Assumed. [1] Heilbron, Jones, McCombie, and Weedon, *loc. cit.* [2] Cymerman, Heilbron, and Jones, *loc. cit.*

Both (I) and (II) and their rearranged isomers are rather unstable in alcoholic acid solution probably owing to accompanying polymerisation and cyclisation reactions. The solutions discolour after $x = ca.\ 0{\cdot}5a$ and only the first 45% of the rearrangements were followed in the determination of $k$'s. The end-values $a$ were assumed in these two cases; the highest values of $E^{1\%}_{1cm.}$ actually reached being about 1500—2000. No chloro-compound formation was ever observed in hydrochloric acid runs, but the rearrangement of (III) in 1·0M-acetic acid on a large scale gave a product which, from refractive index and active hydrogen determinations, contains some of the ethyl ether or di-ether of the isomer. The acid normality of the solution was unchanged, however, indicating that no acetate formation had occurred.

Two representative runs are reproduced below: $c_{ROH}$ = carbinol concentration (% w/v), $c_A$ = acid concentration (mol./l.), $c_{EtOH}$ = alcohol concentration (% by vol.).

Rearrangement of (III), $c_{ROH} = 0{\cdot}7$, $c_A = 0{\cdot}02$M-HCl, $c_{EtOH} = 60$, $t = 40°$.

| Time (mins.). | $E^{1\%}_{1cm.}$ at 2240 A. | $10^4k$ (min.$^{-1}$). | Time (mins.). | $E^{1\%}_{1cm.}$ at 2240 A. | $10^4k$ (min.$^{-1}$). |
|---|---|---|---|---|---|
| 4 | 843 | 1020 | 12 | 1830 | 1050 |
| 8 | 1400 | 1030 | ∞ | 2550 | — |
| | | | | | Mean 1035 |

Rearrangement of (III), $c_{ROH} = 3{\cdot}5$, $c_A = 1$M-AcOH, $c_{EtOH} = 80$, $t = 30°$.

| | | | | | |
|---|---|---|---|---|---|
| 1480 | 407 | 1·40 | 6945 | 1360 | 1·39 |
| 4060 | 970 | 1·44 | ∞ | 2550 * | — |
| | | | | | Mean 1·41 |

* Assumed.

The dissociation constant of *n*-butylpropiolic acid was determined by electrometric titration of 5 ml. of 0·01 M-aqueous solution of the acid with 1 ml. of 0·1 M-potassium hydroxide, a glass electrode being used. The pH value at half-neutralisation was 2·85, hence $K = 0{\cdot}0014$.

## Discussion.

The characteristics of the reaction, such as reaction order, dependence of $k$ on $c_{ROH}$, $c_A$, $c_{EtOH}$, etc., being the same as those found for the corresponding acetylenyl carbinols, the mechanism is clearly analogous to that deduced for the previous series (see p. 126), the terminal ·C:CR$_2$ group being replaced by ·CH:CH$_2$. A reversible oxonium-ion formation is followed by the rate-determining isomerisation, the driving force of the reaction being made up mainly of the tendency of the two ethylenic bonds to enter into conjugation.

Probability factors and relative rate constants are given in Table III, together with the data for the corresponding ethynylcarbinols (Part III, preceding paper). It is evident that there is no obvious correlation between

### Table III.

$r$ = Observed rate constant at 30° in 60% EtOH relative to (III) and (VII), respectively.

| | $10^4k$ in 0·1M-HCl, 60% EtOH, 30°. * | $E_{1D}$ in 60% EtOH. | log $A$. | $r$. | log $r$. |
|---|---|---|---|---|---|
| Vinylcarbinols this paper). | | | | | |
| (I) $CH_2{=}CH{\cdot}CH(OH){\cdot}CH{=}CH_2$ ..... | 1·80 | 29·6 | 15·9 | 0·0010 | −3·0 |
| (II) $CH_2{=}CMe{\cdot}CH(OH){\cdot}CH{=}CH_2$ ..... | 3·28 | 27·9 | 14·8 | 0·0019 | −2·8 |
| (III) $CHMe{=}CH{\cdot}CH(OH){\cdot}CH{=}CH_2$ ..... | *1,730* | 25·2 | 15·7 | 1 | 0 |
| (IV) $CHMe{=}CH{\cdot}CMe(OH){\cdot}CH{=}CH_2$ ..... | *22,000* | 25·4 | 16·9 | 13 | 1·1 |
| Ethynylcarbinols (Part III). | | | | | |
| (V) $CH_2{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH$ ..... | *0·00015* | ~22 | ~6 | 0·0003 | −3·5 |
| (VI) $CH_2{=}CMe{\cdot}CH(OH){\cdot}C{\equiv}CH$ ..... | *0·0011* | ~31 | ~13 | 0·002 | −2·7 |
| (VII) $CHMe{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH$ ..... | 0·54 | 31·4 | 16·6 | 1 | 0 |
| (VIII) $CHMe{=}CH{\cdot}CMe(OH){\cdot}C{\equiv}CH$ ..... | 93 | 28·8 | 17·0 | 160 | 2·2 |

* Extrapolated values in italics.

the values of $E_{[D]}$ and log $A$ in the two series, but the gradation of rate constants is clearly very similar. Methyl substituents facilitate the rearrangement, and, as in the previous series, a substituent in the system $\overset{1}{C}R_1R_2{=}\overset{2}{C}R_3{-}\overset{3}{C}R_4(OH){-}CH{=}CH_2$, has the largest effect when attached to carbon atom 1, a smaller effect when attached to carbon atom 3, and a still smaller effect when attached to carbon atom 2:

| Substituent. | $R_1$ = Me. | $R_3$ = Me. | $R_4$ = Me. |
|---|---|---|---|
| $\Delta \log r$ ..... | 3·0 | 0·2 | 1·1 |

The substituent effects in the two series are thus essentially the same, and this lends additional support to the identity of the reaction mechanisms.

Turning from the similarities to the differences between the two series, some of the latter are tabulated below. The ratio of the rate constants of the two reference compounds ($R_1$ = Me; $R_2 = R_3 = R_4$ = H) under identical

| Substituents. | — | $R_3$ = Me. | $R_1$ = Me. | $R_1 = R_4$ = Me. |
|---|---|---|---|---|
| $k_{\text{vinylcarbinol}}/k_{\text{acetylenylcarbinol}}$ ..... | 12,000 | 3000 | 3200 | 240 |

conditions at 30° is 3200. This ratio is almost unaltered when the single methyl substituent is in a different position ($R_3$ = Me), but it is much larger when no methyl substituents are present and much smaller when there are two. There is thus a very marked decrease of the ratio $k_{\text{vinylcarbinol}}/k_{\text{acetylenylcarbinol}}$ as the number of methyl substituents increases, but the number of compounds so far studied is insufficient to warrant any decision as to the generality of this relationship.

The large differences in rate constants between corresponding compounds [*e.g.*, CHMe=CH·CH(OH)·C≡CH and CHMe=CH·CH(OH)·CH=$CH_2$] of the two series must be considered. These are in no way connected with the presence or otherwise of the acetylenic hydrogen atom, since its replacement (by, *e.g.*, an *n*-Bu group) does not alter the characteristics of the rearrangement (Part III, *loc. cit.*), and since any possible ionisation of the acetylenic hydrogen atom would in any case be suppressed in acid solution. The large increase in the rate constant brought about by the replacement of the acetylenyl by the vinyl group is easily accounted for, however, by the much smaller electron-attracting nature of the vinyl as compared with the acetylenyl carbon atom adjacent to the carbinol group. This electron-attraction arises from the co-ordinative unsaturation of atoms forming multiple linkages and represents a negative inductive effect (cf. Dippy, *Chem. Rev.*, 1939, **25**, 151). The higher the multiplicity of the linkage, *i.e.*, the greater the number of electron pairs shared, the greater is the electron deficiency on the constituent atoms and thus the negative-inductive effect of the acetylenic group would be expected to be much greater than that of the ethylenic group. Both steps involved in the mechanism of the present reaction require electron accession at the reacting centre and are therefore facilitated by the replacement of an acetylenic by an ethylenic group. The reverse is true of the ionisation of a carboxylic acid. The differences in the dissociation constants of propiolic, butylpropiolic, and acrylic acids may be compared with the differences in the rate constants of the rearrangements of propenylethynyl-, propenylhexynyl-, and propenylvinyl-carbinols.

| | $10^4k$ (min.$^{-1}$) in 0·02M-HCl, 60% EtOH at 30°. | | $10^5K$ in water, 25°. |
|---|---|---|---|
| CHMe=CH·CH(OH)·C≡CH ... | 0·11 | CH≡C·$CO_2$H ..... | 1400 [1] |
| CHMe=CH·CH(OH)·C≡CBu(*n*) | 16·5 | CBu≡C·$CO_2$H ..... | 140 |
| CHMe=CH·CH(OH)·CH=$CH_2$ | 345 | $CH_2$=CH·$CO_2$H ..... | 5·5 [2] |

[1] Wilson and Wenzke, *J. Amer. Chem. Soc.*, 1935, **57**, 1265. [2] Dippy, *loc. cit.*

Qualitative evidence for the greater electron-attraction of the acetylenic as compared with the ethylenic group has also been adduced by Baker, Cooper, and Ingold (J., 1928, 426) from a study of the nitration of cinnamic and phenylpropiolic acids.

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## 37. *The Preparation of Phenyl (α-Ethyl-α-n-decyl)-n-tridecyl Ketone (ω-Ethyl-ω-n-decyl-ω-n-dodecylacetophenone) and Related Substances.*

By C. L. CARTER and S. N. SLATER.

The preparation of ethyldecyldodecylacetophenone and a number of trialkylacetic acids by Haller's sodamide method is described. A small alkyl group is introduced into the aliphatic chain of one of the higher homologues of acetophenone, and the product alkylated with a long-chain alkyl iodide.

WITHIN recent years the isolation of physiologically active fatty acids containing branched chains has stimulated work in this field. In particular the suggestion that phthioic acid, isolated by Anderson and co-workers from *M. Tuberculosis*, might be a trialkylacetic acid (Stenhagen and Stallberg, *J. Biol. Chem.*, 1941, **139**, 345) has led to the exploration of methods for preparing such substances (see especially Robinson *et al.*, *J.*, 1942, 488; 1943, 615; 1944, 152). One of the few earlier methods was that of Haller and Bauer (*Ann. Chim.*,

1914, **1**, 5) in which a phenyl alkyl ketone is alkylated in the α-position by means of sodamide and an alkyl iodide to give an ω-trialkylacetophenone which is then decomposed by sodamide into a trialkylacetamide, from which the acid is obtained by nitrous acid.

Haller's method gives good yields of the simpler acids of this series, but difficulty has been experienced in preparing the higher members. Thus Birch and Robinson (*J.*, 1942, 490) were unable to prepare ω-methyl-ωω-di-*n*-decylacetophenone by methylation of ωω-di-*n*-decylacetophenone and state that "all attempts to alkylate acetophenones substituted in the ω-position by two long-chain alkyls were unsuccessful." Buu-Hoï and Cagniant (*Ber.*, 1943, **76**, 689) attempted to prepare ω-ethyl-ω-*n*-decylacetophenone by condensation of α-ethyl-lauryl chloride with benzene and aluminium chloride but obtained a viscous inseparable mixture, richer in carbon, of several ketone-like compounds. In preparing such ω-trialkylacetophenones it would appear to be more reasonable to introduce a small alkyl group into one of the higher homologues of acetophenone and then alkylate with a long-chain alkyl iodide. By this method, *phenyl (α-ethyl-α-n-decyl)-n-tridecyl ketone* (*ω-ethyl-ω-n-decyl-ω-n-dodecylacetophenone*) was prepared without difficulty by acting upon *phenyl (α-ethyl)-n-undecyl ketone* (*ω-ethyl-ω-n-decylacetophenone*) with sodamide and *n*-dodecyl iodide. The corresponding acid, however, was not obtained, except possibly in small amount in an impure state, by heating the ketone with sodamide and treating the product with nitrous acid. The main acidic product isolated was benzoic acid.

In order to gain some idea of the scope of the Haller method a number of lower trialkylacetic acids* were prepared. One alkyl group was restricted to one or two carbon atoms, and the other two were successively lengthened. No difficulty was experienced in preparing all the acids of this series up to $C_{10}H_{20}O_2$. In the $C_{11}H_{22}O_2$ group the formation of benzoic acid instead of the required fatty acid became noticeable. Thus α-methyl-α-ethyl-*n*-octoic acid was not obtained pure, and an attempted preparation of αα-diethyl-*n*-heptoic acid yielded mainly benzoic acid. On the other hand α-methyl-α-butyl-*n*-hexoic acid and *α-ethyl-α-propyl-n-hexoic acid* were prepared satisfactorily, and Grunfeld (*Ann. Chim.*, 1933, **20**, 304) has synthesised αα-dimethyl-*n*-nonoic acid by Haller's method. In the $C_{12}H_{24}O_2$ group, αα-dimethyl-*n*-decoic acid was prepared, but much benzoic acid was formed in the preparation of αα-diethyl-*n*-octoic acid, and an attempted preparation of α-ethyl-α-propyl-*n*-heptoic acid gave mainly benzoic acid. In the $C_{13}H_{26}O_2$ group, *α-methyl-α-butyl-n-octoic acid* and *αα-diethyl-n-nonoic acid* were prepared, but the attempted preparation of α-ethyl-α-propyl-*n*-octoic acid and α-ethyl-α-butyl-*n*-heptoic acid gave mainly benzoic acid. In the $C_{14}H_{28}O_2$ group, αα-dimethyl-*n*-dodecoic acid has been prepared (Haller and Bauer, *loc. cit.*; Birch and Robinson, *loc. cit.*), but an attempted preparation of α-ethyl-α-butyl-*n*-octoic acid gave mainly benzoic acid. In the $C_{15}H_{30}O_2$ group, *α-ethyl-α-butyl-n-nonoic acid*, accompanied by much benzoic acid, was obtained, and the main product of an attempted preparation of α-ethyl-α-amyl-*n*-octoic acid was benzoic acid. In the $C_{16}H_{32}O_2$ group, a small yield of *α-ethyl-α-butyl-n-decoic acid* was obtained. In the $C_{17}H_{34}O_2$ group, attempted preparations of α-methyl-α-butyl-*n*-dodecoic acid and α-ethyl-α-amyl-*n*-decoic acid gave mainly benzoic acid. A similar result was obtained in the case of α-ethyl-α-butyl-*n*-dodecoic acid in the $C_{18}H_{36}O_2$ group. Higher in the series, αα-dimethyl-*n*-tetradecoic acid (Buu-Hoï and Cagniant, *Z. physiol. Chem.*, 1943, **279**, 76), αα-dimethylpalmitic acid (*idem*, *ibid.*), αα-dimethylstearic acid (Birch and Robinson, *loc. cit.*), and αα-dimethylarachidic acid (Buu-Hoï and Cagniant, *loc. cit.*) have been prepared.

It appears therefore that while dimethylalkylacetic acids can be successfully prepared, even when the alkyl group attains to a length of eighteen carbon atoms, the Haller method may fail with acids of much lower molecular weight but greater complexity as measured by the length of all three substituent groups.

## Experimental.

Haller's preparations of dimethylethylacetic acid (αα-dimethyl-*n*-butyric acid), b. p. 184—186° (184—185°), dimethylpropylacetic acid (αα-dimethyl-*n*-valeric acid), b. p. 199—205° (199—200°; Tafel and Emmert, *Z. Elektrochem.*, 1911, **17**, 571, 200—205°), methyldiethylacetic acid (α-methyl-α-ethyl-*n*-butyric acid), b. p. 202—206° (203—204°; Schdanow, *Annalen*, 1877, **185**, 120, 207—208°), methylethylpropylacetic acid (α-methyl-α-ethyl-*n*-valeric acid), b. p. 215—224° (215—220°), and triethylacetic acid, b. p. 211—215° (220—222°) were repeated. Except where otherwise indicated the figures in parenthesis are the b. ps. given by Haller.

*αα-Dimethyl-n-hexoic acid.* This and the following acid have not previously been made by Haller's method. Propiophenone (27 g.) was successively methylated (sodamide, 8 g., methyl iodide, 29 g., in benzene) and butylated (sodamide, 8 g., butyl iodide, 38 g.) and worked up to give a product, b. p. 140—153°/28 mm. (total distillate collected, 20·5 g.). Treated with sodamide (6·0 g.) in boiling benzene this gave the amide (8·0 g.), b. p. 140—145°, m. p. (from benzene–ligroin) 88—89°. The amide in concentrated sulphuric acid was cooled in a freezing mixture while excess of a cold, saturated solution of sodium nitrite was slowly stirred in; the product was warmed, diluted with water, and extracted with ether. The ethereal extract was shaken with three successive portions of 2N-sodium hydroxide and the combined alkaline extracts acidified. The liberated acid was extracted with chloroform and distilled (1·6 g., b. p. 210—218°).

*αα-Dimethyl-n-heptoic acid.* Phenyl *n*-hexyl ketone (14 g.) was methylated twice to phenyl αα-dimethylhexyl ketone (15 g.), b. p. 148—150°/18 mm., which was split with sodamide to the amide (8 g.), b. p. 147—149°/19 mm., which solidified readily. A sample crystallised from benzene had m. p. 101°. The amide (7 g.) was converted to the acid (3·0 g.), b. p. 124—127°/21 mm., together with a small residue of benzoic acid (Leers, *Bull. Soc. chim.*, 1926, **39**, 651, gives 101—102° as the m. p. of the amide, but the b. p. given for the acid, 130°/12 mm., appears to be too high for a $C_9$ trialkylacetic acid judged by the b. ps. of the other isomers).

*α-Methyl-α-ethyl-n-hexoic Acid.*—Phenyl *sec.*-butyl ketone (9·7 g.) was alkylated with sodamide (2·4 g.) and butyl iodide (12 g.) and the total distillate (11·1 g.), b. p. 132—152°/18 mm., refluxed with sodamide in benzene to give the crude amide (7·8 g.), b. p. 124—144°/18 mm. On treatment with nitrous acid the *acid* (1·9 g.) was obtained, b. p. 123—125°/22 mm. (Found: C, 69·0; H, 11·4. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%).

* These have been systematically named. The authors emphasised that the compounds are trialkyl substituted acetic acids; systematically, they are αα-di-*n*-alkyl substituted acids of the $n$-$C_nH_{2n+1}CO_2H$ series. (Temp. Editor.)

*α-Methyl-α-propyl-n-valeric acid.* This was made by Haller's method. Propiophenone was treated twice with sodamide and propyl iodide and the product, b. p. 144—152°/23 mm., split with sodamide to give the crude amide, b. p. 145—153°/25 mm. On treatment with nitrous acid the required acid was obtained, b. p. 126—129°/29 mm. Meerwein (*Annalen*, 1919, **419**, 141) gives b. p. 118—122°/14 mm.

*αα-Diethyl-n-valeric Acid.*—Butyrophenone was successively ethylated and propylated and the product (34·8 g.), b. p. 147—155°/27 mm., split with sodamide to give the crude amide (10·5 g.), b. p. 144—153°/26 mm. On treatment with nitrous acid the required *acid* (3·9 g.) was obtained, b. p. 128°/29 mm. (Found: C, 67·6; H, 11·1. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%).

*αα-Dimethyl-n-octoic Acid.*—Phenyl *n*-heptyl ketone (30 g.) was methylated twice and the product (14 g.), b. p. 165°/17 mm., split with sodamide to give the amide (8·8 g.), b. p. 162°/22 mm., which solidified on cooling; it had m. p. 103—104° (from benzene). Treatment of the amide (6 g.) with nitrous acid gave the required *acid* (3·0 g.), b. p. 135—138°/21 mm. (Found: C, 69·9; H, 11·9. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

*α-Methyl-α-ethyl-n-heptoic Acid.*—Phenyl *n*-hexyl ketone (14 g.) was successively methylated and ethylated and the product (14 g.), b. p. 179—182°/26 mm., split with sodamide to give the crude amide (8 g.), b. p. 147—153°/19 mm. On treatment with nitrous acid this furnished the required *acid* (2·9 g.), b. p. 131—135°/21 mm. (Found: C, 69·1; H, 11·1. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

*α-Methyl-α-propyl-n-hexoic Acid.*—Phenyl *n*-amyl ketone (35 g.) was successively methylated and propylated and the product (37 g.), b. p. 149—155°/18 mm., split with sodamide to give the crude amide (25·7 g.), b. p. 145—152°/20 mm. On treatment with nitrous acid this furnished the required *acid* (2·8 g. from 10 g. of crude amide), b. p. 141—143°/29 mm. (Found: C, 69·4; H, 11·4. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

*αα-Diethyl-n-hexoic Acid.*—Butyrophenone (25 g.) was successively ethylated and butylated and the product (26·2 g.), b. p. 160—170°/29 mm., split with sodamide to give the crude amide (10 g.), b. p. 153—164°/26 mm. Treatment of this with nitrous acid gave the *acid* (2·4 g.), b. p. 137—141°/21 mm. On redistillation, it had b. p. 135°/25 mm. (Found: C, 69·4; H, 11·4. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

*α-Ethyl-α-propylvaleric Acid.*—Butyrophenone (30 g.) was propylated twice and the product (37·9 g.), b. p. 155—164°/27 mm., split with sodamide to give the crude amide (13·2 g.), b. p. 153—162°/27 mm. When treated with nitrous acid this gave the required *acid* (4·3 g.), b. p. 138—144°/25 mm. On redistillation, it had b. p. 132°/22 mm. (Found: C, 69·3; H, 11·7. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

*α-Methyl-α-ethyl-n-octoic Acid.*—Phenyl *n*-heptyl ketone (15 g.) was successively methylated and ethylated and the product (16 g.), b. p. 167—169°/21 mm., refluxed with sodamide (9 g.) in benzene giving a product (12·3 g.), b. p. 152—162°/18 mm., which partly solidified. Treatment with nitrous acid yielded a mixture of acids distilling over a fairly wide range. On standing the product partly crystallised. It was redistilled giving a liquid acid (2·6 g.), b. p., 135—140°/19 mm. A portion, b. p. 135—137°/19 mm., was collected for analysis (Found: C, 68·0; H, 8·9. Calc. for $C_{11}H_{22}O_2$: C, 71·0; H, 11·8%).

*α-Methyl-α-butyl-n-hexoic acid.* This has not previously been made by Haller's method. Propiophenone (16 g.) was butylated twice and the product (21·3 g.), b. p. 156—168°/18 mm., split with sodamide to give the crude amide (9·3 g.), b. p. 163—169°/25 mm. When this was treated with nitrous acid the required acid (3·2 g.) was obtained, b. p. 144—147°/20 mm. On redistillation, it had b. p. 144°/22 mm. (Found: C, 70·5; H, 11·9. Calc. for $C_{11}H_{22}O_2$: C, 71·0; H, 11·8%). Meerwein, *loc. cit.*, gives b. p. 158—159°/18 mm. which appears to be high.

*α-Ethyl-α-propyl-n-hexoic Acid.*—Butyrophenone (16 g.) was successively propylated and butylated and the product (14 g.), b. p. 149—162°/22 mm., split with sodamide to give the crude amide (8·7 g.), b. p. 142—160°/22 mm. On treatment with nitrous acid this gave the required *acid* (1·4 g.), b. p. 135—137°/22 mm. (Found: C, 70·1; H, 12·0. $C_{11}H_{22}O_2$ requires C, 71·0; H, 11·8%).

*αα-Dimethyl-n-decoic acid.* This has not previously been made by Haller's method. *iso*Butyrophenone was alkylated with sodamide and *n*-octyl iodide and the product, b. p. 190°/25 mm., split with sodamide to give the amide, b. p. 191—193·5°/25 mm. When this was treated with nitrous acid the required acid, b. p. 153—158°/19 mm., was obtained.

*Attempted preparation of αα-diethyl-n-octoic acid.* (*a*) Phenyl *n*-heptyl ketone (14 g.) was treated with sodamide (3 g.) and ethyl iodide (12 g.) and the product (14 g.), b. p. 157—162°/19 mm., subjected to the same treatment giving 11 g. of an oily ketone, b. p. 167—173°/17 mm. This was split with sodamide (8 g.) to yield the crude amide (9 g.), b. p. 167—169°/18 mm. Treatment with nitrous acid furnished a liquid acid (2·4 g.) having the expected b. p. (156—163°/18 mm., portion b. p. 160—162° collected for analysis), but satisfactory analytical figures were not obtained (Found: C, 68·7, 68·8; H, 11·2, 11·1%).

(*b*) Phenyl α-ethylpropyl ketone was treated with sodamide and *n*-hexyl iodide in the usual manner and the product, boiling over a wide range, was heated with sodamide in benzene to give a mixture of amides which with nitrous acid furnished a mixture of much benzoic acid and liquid fatty acids boiling over a wide range (up to 174°/24 mm.). The material distilling at 140—158° solidified on cooling, while that distilling at 158—174° contained a greater proportion of liquid acid. It was filtered and the small quantity of filtrate redistilled. Analysis of a sample of the middle portion of this distillate gave figures well removed from the theoretical (Found: C, 73·2; H, 10·5%).

*α-Methyl-α-butyl-n-octoic Acid.*—Phenyl *n*-heptyl ketone (15 g.) was successively methylated and butylated and the product (11 g.), b. p. 175—183°/17 mm., split with sodamide to give the amide (9 g.), b. p. 167—169°/18 mm. This was treated with nitrous acid to give the required *acid* (2·4 g.), b. p. 156—163°/18 mm. On redistillation, it had b. p. 160—162°/18 mm. (Found: C, 73·4; H, 12·3. $C_{13}H_{26}O_2$ requires C, 72·9; H, 12·2%).

*αα-Diethyl-n-nonoic Acid.*—Phenyl *n*-octyl ketone (12 g.) was ethylated twice and the product (11 g.), b. p. 175—185°/16 mm., split with sodamide to give the crude amide (8 g.), b. p. 180—185°/24 mm. This was treated with nitrous acid to furnish the required *acid* (1·9 g.), b. p. 158—163°/16 mm. (Found: C, 72·6; H, 12·2. $C_{13}H_{26}O_2$ requires C, 72·9; H, 12·2%).

*α-Ethyl-α-butyl-n-nonoic Acid.*—Phenyl *n*-octyl ketone (12 g.) was successively ethylated and butylated and the product (11 g.), b. p. mainly 190—195°/16 mm., refluxed with sodamide to give the crude amide (9 g.), b. p. mainly 175—182°/18 mm. When this was treated with nitrous acid a product was obtained which after distillation solidified in part and contained benzoic acid. It was redistilled and the required *acid* (1·4 g.) obtained as the fraction, b. p. 165—172°/16 mm. (Found: C, 74·1; H, 12·0. $C_{15}H_{30}O_2$ requires C, 74·3; H, 12·5%).

*α-Ethyl-α-butyl-n-decoic Acid.*—Phenyl *n*-amyl ketone (75 g.) was ethylated and the product (68 g.), b. p. 149—151°/19 mm., alkylated with sodamide (13·2 g.) and *n*-octyl iodide (82 g.) to give 50 g. of material, b. p. 204—210°/16 mm. This was refluxed with sodamide (20 g.) in xylene and the product worked up to furnish a small yield of an oil giving a positive test for nitrogen together with recovered material (29 g.). This was treated again in boiling xylene solution with sodamide to give an oil boiling over rather a wide range. All fractions gave a positive test for nitrogen and the total distillate was therefore treated with nitrous acid and worked up to give a small yield of *acid*, b. p. 175—195°/16 mm. This was redistilled and a portion of the middle distillate analysed (Found: C, 75·5; H, 12·3. $C_{16}H_{32}O_2$ requires C, 74·9; H, 12·6%).

*Phenyl (α-Ethyl-α-n-decyl)-n-tridecyl Ketone (Ethyl-n-decyl-n-dodecylacetophenone).*—Phenyl *n*-undecyl ketone (52 g.,)

b. p. 214—218°/24 mm., and sodamide (8 g.) were refluxed for 6 hours in benzene, and ethyl iodide (35 g.) added. After heating overnight the *phenyl* (*α-ethyl*)-n-*undecyl ketone* (*ethyl*-n-*decylacetophenone*) (47 g., b. p. mainly 211°/16 mm.) was obtained in the usual way (Found: C, 82·6; H, 11·5. $C_{20}H_{32}O$ requires C, 83·3; H, 11·1%). This ketone (47 g.) was treated with sodamide (6·5 g.) and *n*-dodecyl iodide (48·3 g.) in benzene to give *phenyl* (*α-ethyl-α*-n-*decyl*)-n-*tridecyl ketone* (*ethyl*-n-*decyl*-n-*dodecylacetophenone*) (33 g.), b. p. 240—252°/1 mm., and in a second preparation 240—246°/1 mm. A portion of the middle distillate was collected for analysis (Found: C, 84·4; H, 12·3. $C_{32}H_{56}O$ requires C, 84·2; H, 12·3%). Treatment of the ketone with sodamide gave a product boiling over a wide range (up to 285° under high vacuum), and interaction of this with nitrous acid yielded a mixture of benzoic and other acids from which a small amount of a liquid fatty acid was isolated whose composition approximated to that of the desired $C_{24}$ acid (Found: C, 80·7; H, 11·7. Calc. for $C_{24}H_{52}O_2$: C, 78·8; H, 13·1%).

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## 38. *Physical Properties and Chemical Constitution. Part IX. Aliphatic Hydrocarbons.*

By ARTHUR I. VOGEL.

New experimental data for the parachors and refractivities of the normal hydrocarbons (*n*-pentane to *n*-hexadecane) and certain branched-chain hydrocarbons are presented. The data for the normal paraffins give for $CH_2$, *P* 39·98, $R_C$ 4·618, $R_D$ 4·643, $R_F$ 4·687, $R_{G'}$ 4·731, and $Mn_D^{20°}$ 20·63. By combining these figures with those deduced in Part VIII (J., 1943, 638), the following figures for $CH_2$, H, and C (in $CH_2$) have been obtained:

| | *P*. | $R_C$. | $R_D$. | $R_F$. | $R_{G'}$. | $Mn_D^{20°}$. |
|---|---|---|---|---|---|---|
| $CH_2$ | 40·02 | 4·624 | 4·647 | 4·695 | 4·735 | 20·59 |
| H | 15·7 | 1·026 | 1·028 | 1·043 | 1·040 | −2·56 |
| C (in $CH_2$) | 8·6 | 2·572 | 2·591 | 2·601 | 2·655 | 25·71 |

In Part VIII (*loc. cit.*) it was pointed out that the new data for *n*-alkyl halides led to the following values for $CH_2$ differences when evaluated by the method of least squares:

| | *P*. | $R_C$. | $R_D$. | $R_F$. | $R_{G'}$. | $Mn_D^{20°}$. |
|---|---|---|---|---|---|---|
| Chlorides | 40·10 | 4·621 | 4·641 | 4·691 | 4·734 | 20·71 |
| Bromides | 40·02 | 4·625 | 4·646 | 4·696 | 4·733 | 20·79 |
| Iodides | 39·98 | 4·631 | 4·656 | 4·707 | 4·743 | 20·24 |

These values differed so seriously from the hitherto accepted figures (*P* 39·0, Sugden, J., 1924, **125**, 1180; $R_C$ 4·598, $R_D$ 4·618, $R_F$ 4·668, $R_{G'}$ 4·710, Eisenlohr, *Z. physikal. Chem.*, 1911, **75**, 605; $Mn_D^{20°}$ 20·56, *Fortschr. Chem. Physik, u. physikal. Chem.*, 1925, Band *18*, Heft 9, p. 5) that a thorough reinvestigation was deemed desirable. Moreover, since the atomic and structural parachors and refractivities, as computed by Sugden and by Eisenlohr respectively, are based upon the values of the $CH_2$ grouping, any change in the magnitudes of the latter constants will, of necessity, require recalculation of all the atomic and structural constants.

The normal hydrocarbons, *n*-pentane to *n*-hexadecane, have been prepared in a high degree of purity and their parachors and refractivities determined.* The results are summarised in Table I; molecular refractivities refer to a temperature of 20°. The mean values of the $CH_2$ increments were calculated, using the data for *n*-pentane as standard, by the method of least squares. These results provide independent confirmation of those obtained in Part VIII from the experimental figures upon *n*-alkyl chlorides, bromides, and iodides, and suggest that both Sugden's and Eisenlohr's atomic and structural constants require revision.

TABLE I.

*Parachors and refractivities of normal hydrocarbons.*

| | *P*. | $R_C$. | $R_D$. | $R_F$. | $R_{G'}$. | $Mn_D^{20°}$ |
|---|---|---|---|---|---|---|
| $C_5H_{12}$ | 231·8 | 25·16 | 25·28 | 25·55 | 25·73 | 97·98 |
| $C_6H_{14}$ | 270·9 | 29·79 | 29·93 | 30·25 | 30·47 | 118·49 |
| $C_7H_{16}$ | 312·0 | 34·44 | 34·60 | 34·97 | 35·24 | 139·04 |
| $C_8H_{18}$ | 350·5 | 39·00 | 39·17 | 39·60 | 39·90 | 159·61 |
| $C_9H_{20}$ | 390·7 | 43·66 | 43·85 | 44·33 | 44·69 | 180·24 |
| $C_{10}H_{22}$ | 429·9 | 48·28 | 48·50 | 49·03 | 49·40 | 200·91 |
| $C_{11}H_{24}$ | 470·6 | 52·92 | 53·15 | 53·72 | 54·13 | 221·51 |
| $C_{12}H_{26}$ | 510·0 | 57·45 | 57·71 | 58·32 | 58·77 | 242·19 |
| $C_{13}H_{28}$ | 550·5 | 62·14 | 62·41 | 63·09 | 63·56 | 262·77 |
| $C_{14}H_{30}$ | 591·4 | 66·79 | 67·10 | 67·81 | 68·34 | 283·50 |
| $C_{15}H_{32}$ | 631·3 | 71·35 | 71·67 | 72·44 | 73·02 | 304·17 |
| $C_{16}H_{34}$ | 671·3 | 75·92 | 76·27 | 77·07 | 77·66 | 324·86 |
| *Mean values for* $CH_2$ *calculated by the method of least squares.* | | | | | | |
| $CH_2$ | 39·98 | 4·618 | 4·643 | 4·687 | 4·731 | 20·63 |

* The author's work was completed in September 1939, but publication was not considered desirable during the period of hostilities. Quayle, Day, and Brown (*J. Amer. Chem. Soc.*, 1944, **66**, 938) have determined the densities and surface tensions (maximum bubble pressure method), chiefly at 20°, 30°, and 40°, of the normal hydrocarbons, *n*-pentane to *n*-duodecane, but the method of preparation of the hydrocarbons is not given. The parachors are in good agreement with those obtained in the present work (capillary rise method) and lead to an average $CH_2$ increment of 40·0. Mumford and Phillips (J., 1929, 2112) had put forward a value of 40, based upon the data upon fatty acids by Hunten and Maass (*J. Amer. Chem. Soc.*, 1929, **51**, 153) and the normal hydrocarbons $C_{28}H_{54}$, $C_{32}H_{66}$, and $C_{60}H_{122}$.

The average values for $CH_2$ deduced by the method of least squares from the data on *n*-hydrocarbons, *n*-alkyl chlorides, bromides and iodides are *P* 40·02, $R_C$ 4·624, $R_D$ 4·647, $R_F$ 4·695, $R_{G'}$ 4·735, $Mn_D^{20°}$ 20·59. These figures will be employed in all calculations.

It is of interest to compare the individual variations in the four homologous series used by the author in the computation of the mean $CH_2$ contributions with those utilised by Eisenlohr (*loc. cit.*) for a similar purpose.

*Eisenlohr's data for* $CH_2$.

| | $R_C$. | $R_D$. | $R_F$. | $R_{G'}$. | | $R_C$. | $R_D$. | $R_F$. | $R_{G'}$. |
|---|---|---|---|---|---|---|---|---|---|
| Hydrocarbons ..... | 4·6054 | 4·6247 | 4·6783 | 4·7233 | Alcohols ..... | 4·6141 | 4·6343 | 4·6849 | 4·7265 |
| Aldehydes and ketones | 4·6064 | 4·6265 | 4·6757 | 4·7136 | Esters ..... | 4·5863 | 4·6056 | 4·6561 | 4·6961 |
| Acids ..... | 4·5911 | 4·6137 | 4·6617 | 4·7139 | Mean ..... | 4·5977 | 4·6178 | 4·6861 | 4·7102 |

The large variations in the different series are noteworthy, and it is questionable whether Eisenlohr's mean values possess any serious significance when expressed to four (or five) significant figures.

The atomic constants for hydrogen have been determined by two procedures: (*a*) From $C_nH_{2n+2} - nCH_2$ as applied to each normal hydrocarbon, and the mean value taken. (*b*) By comparing *n*-$C_5H_{12}$ and *n*-$C_6H_{11}$ (= 0·5 × *n*-$C_{10}H_{22}$), *n*-$C_6H_{14}$ and *n*-$C_8H_{13}$, *n*-$C_7H_{16}$ and *n*-$C_7H_{15}$, and *n*-$C_8H_{18}$ and *n*-$C_8H_{17}$, and averaging the results. The latter method requires no knowledge of the $CH_2$ contribution. The average figures obtained by both methods are given in Table II.

TABLE II.

*Atomic constants for hydrogen.**

| | *P*. | $R_C$. | $R_D$. | $R_F$. | $R_{G'}$. | $Mn_D^{20°}$. |
|---|---|---|---|---|---|---|
| $C_nH_{2n+2} - nCH_2$ ..... | 15·4 | 1·012 | 1·011 | 1·026 | 1·014 | −2·46 |
| $C_nH_{2n+2} - C_nH_{2n+1}$ ..... | 16·0 | 1·040 | 1·045 | 1·060 | 1·065 | −2·66 |
| Mean ..... | 15·7 | 1·026 | 1·028 | 1·043 | 1·040 | −2·56 |

* The accurate measurements of the refractive indices for the normal hydrocarbons (*n*-pentane to *n*-duodecane) by Shepard *et al.* (*loc. cit.*; see Experimental), with the author's mean values for $CH_2$, give for hydrogen $R_C$ 1·009, $R_D$ 1·008, and $R_F$ 1·034, whilst the determinations of Wibaut *et al.* (*loc. cit.*) for *n*-pentane to *n*-nonane lead to $R_C$ 1·002, $R_D$ 1·001, $R_F$ 1·020, and $R_{G'}$ 1·034.

The atomic constants for carbon in $CH_2$ are therefore ($CH_2$ − 2H) *P* 8·6, $R_C$ 2·572, $R_D$ 2·591, $R_F$ 2·601, $R_{G'}$ 2·655, and $Mn_D^{20°}$ 25·71.

Sugden (*loc. cit.*) found C, 4·8 and H, 17·1, whilst Eisenlohr (*loc. cit.*) deduced for hydrogen $R_C$ 1·092, $R_D$ 1·110, $R_F$ 1·115, $R_{G'}$ 1·122, and for carbon $R_C$ 2·413, $R_D$ 2·418, $R_F$ 2·438, and $R_{G'}$ 2·466. Eisenlohr's values for hydrogen were evaluated from the existing data upon the hydrocarbons (hexane, octane, decane, and di*iso*amyl) and a number of alcohols. These are given as:

| | $R_C$. | $R_D$. | $R_F$. | $R_{G'}$. | | $R_C$. | $R_D$. | $R_F$. | $R_{G'}$. |
|---|---|---|---|---|---|---|---|---|---|
| 2H from hydrocarbons | 2·2601 | 2·2704 | 2·3016 | 2·3170 | Mean 2H ..... | 2·1848 | 2·1998 | 2·2306 | 2·2447 |
| 2H from alcohols ..... | 2·1093 | 2·1292 | 2·1597 | 2·1723 | Mean H ..... | 1·0924 | 1·0999 | 1·1153 | 1·1224 |

By subtracting the above mean values for 2H from $CH_2$, the figures for carbon were obtained. No further comments are necessary on the possible inaccuracies in Eisenlohr's constants.

The results for a number of branched-chain hydrocarbons are summarised in Table III. These will be utilised in subsequent papers of this series.

TABLE III.

*Branched-chain aliphatic hydrocarbons.*

| | *P*. | $R_C$. | $R_D$. | $R_F$. | $R_{G'}$. | $Mn_D^{20°}$. |
|---|---|---|---|---|---|---|
| 3 : 4-Dimethylhexane (di-*sec*.-butyl) ..... | 342·3 | 38·66 | 38·84 | 39·25 | 39·55 | 160·42 |
| 2 : 5-Dimethylhexane (di*iso*butyl) ..... | 347·5 | 39·06 | 39·24 | 39·68 | 39·98 | 159·07 |
| 2 : 6-Dimethylheptane (di*iso*butylmethane) ..... | 386·5 | 43·68 | 43·88 | 44·35 | 44·71 | 179·65 |
| 2 : 7-Dimethyloctane (di*iso*amyl, " synthetic ") * ..... | 425·1 | 48·19 | 48·39 | 48·92 | 49·30 | 200·60 |
| 2 : 7-Dimethyloctane (di*iso*amyl, " fermentation ") † ... | 426·1 | 48·34 | 48·56 | 49·08 | 49·46 | 200·41 |
| 4 : 5-*Dimethyloctane* ..... | 419·4 | 47·79 | 48·00 | 48·51 | 48·88 | 201·65 |
| 3 : 4-*Diethylhexane* ..... | 417·0 | 47·63 | 47·85 | 48·34 | 48·71 | 201·90 |

* From synthetic *iso*amyl alcohol. † From fermentation *iso*amyl alcohol.

Succeeding papers of this series will be devoted to the provision of new data for different classes of organic compounds, and the evaluation of atomic and structural constants with the aid of the experimental figures for the hydrocarbons.

## EXPERIMENTAL.

*Physical Measurements.*—Full details are given in Part VII (J., 1943, 18). Surface tensions were measured by the method of capillary rise, and only the values for *H* (= *h* − 0·24 mm.) are given. Unless otherwise stated, all b. p.'s are corrected.

*Previous Work.*—Reference will be made to what appear to be the most trustworthy recorded values of the parachor and refractive indices. Unless otherwise indicated, refractive indices and densities ($d_4^{20°}$) refer to a temperature of 20°. Where the method of preparation differs from that used in the present work, it will be briefly stated. The *n*-paraffin hydrocarbons obtained by Shepard, Henne, and Midgley (*J. Amer. Chem. Soc.*, 1931, **53**, 1948) were isolated by careful

fractionation of a special gasoline; the preparation of the hydrocarbons employed by Quayle, Day, and Brown (*loc. cit.*) in their parachor determinations is not described.

**99.*** n-*Pentane*. The method detailed in *Organic Syntheses*, 1931, **11**, 85 was modified as follows. Into a 2-litre, three-necked flask, equipped with a 25-cm. double-surface condenser, a mercury-sealed mechanical stirrer and a thermometer, were placed 60·7 g. of magnesium turnings and a crystal of iodine. Part of a solution of 2-bromopentane (VIII, **76**) in 250 ml. of *n*-butyl ether (dried over anhydrous magnesium sulphate) was placed in a separatory funnel (protected by a calcium chloride guard tube) supported in the top of the double-surface condenser by means of a grooved cork. About 35 ml. of the bromide solution were run on to the magnesium in the flask immersed in a water-bath at about 80° : an extremely vigorous reaction set in after 5 minutes and the liquid refluxed in the condenser. The remainder of the solution of 2-bromopentane in *n*-butyl ether was then added at such a rate that the temperature inside the flask was maintained at 50—60°; careful watching is required during the addition as the reaction becomes vigorous from time to time and external cooling is necessary. After the addition was complete, the mixture was heated on a steam-bath for 1 hour. A 2-litre, three-necked flask was fitted with a separatory funnel having a wide-bored tap, a mercury-sealed mechanical stirrer, a still-head connected to two double-surface condensers in series and set for downward distillation; the receiver was cooled in ice. The flask was charged with a solution of 75 ml. of concentrated sulphuric acid and 500 ml. of water, the stirrer started and half of the solution of the Grignard reagent (this contained much sludge) added during 2 hours; the reaction mixture was then heated on a water-bath until no more pentane distilled. The decomposition was repeated with the other half of the Grignard reagent. The combined distillates were dried (anhydrous magnesium sulphate) and distilled through a four-section Pyrex Young and Thomas column, and the crude *n*-pentane (95 g.) was collected at 33—36° : *n*-butyl ether remained in the flask. The crude pentane was washed repeatedly with 10 ml. portions of concentrated sulphuric acid until the acid remained colourless (7 washings), then successively with water, 10% sodium carbonate solution, and water, and dried with anhydrous magnesium sulphate. It was then distilled from sodium in a Claisen flask with a fractionating side arm; practically all passed over at 36·1°/763 mm., and a middle portion was used for the physical measurements. B. p. 36·1°/763 mm.; $M$ 72·15; $n_C$ 1·35616, $n_D$ 1·35796, $n_F$ 1·36225, $n_G$ 1·36518. Densities determined : $d_{4^\circ}^{20^\circ}$ 0·6269, $d_{4^\circ}^{19\cdot8^\circ}$ 0·6348. Apparatus *D*.

| *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | *γ*. | *P*. | *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | *γ*. | *P*. |
|---|---|---|---|---|---|---|---|---|---|
| 11·2° | 10·89 | 0·6345 | 17·06 | 231·8 | 21·8° | 10·48 | 0·6254 | 16·18 | 232·0 |
| 13·2 | 10·76 | 0·6328 | 16·82 | 231·6 | | | | Mean | 231·8 |

Shepard *et al.* (*J. Amer. Chem. Soc.*, 1931, **53**, 1948) give b. p. 36·00°, $d$ 0·62632, $n_C$ 1·35581, $n_D$ 1·35769, $n_F$ 1·36208. Mair (*Bur. Stand. J. Res.*, 1932, **9**, 457), for *n*-pentane obtained by hydrogenation of pentene over nickel at 140°, gives b. p. 36·06°, $n_D^{25^\circ}$ 1·35470. Wibaut *et al.* (*Rec. Trav. chim.*, 1939, **58**, 337), for *n*-pentane prepared by hydrogenation of pentene, give b. p. 35·95°, $d$ 0·62624, $n_C$ 1·35587, $n_D$ 1·35769, $n_F$ 1·36200, $n_G$ 1·36561, $P$ 230·7.† Quayle *et al.* (*J. Amer. Chem. Soc.*, 1944, **66**, 940) give $d$ 0·6260, $P$ 231·0.

**100.** n-*Hexane*. *Method* 1. 46 G. of clean sodium pieces were placed in a 1·5-litre Pyrex round-bottomed flask fitted with two 25-cm. double-surface condensers in series, and 123 g. of dry *n*-propyl bromide (VIII, **69**) were weighed out separately. About 25 g. of the *n*-propyl bromide were added to the sodium : there was no immediate reaction. The mixture was refluxed gently and within a few minutes the sodium became blue; the reaction commenced and proceeded steadily whilst the blue colour slowly deepened. The flame was removed and the remainder of the *n*-propyl bromide was added in *ca.* 10 ml. portions during 90 minutes with frequent vigorous shaking of the flask. The reaction proceeded steadily for 2—3 hours. After the mixture had been left overnight, 150 ml. of rectified spirit were added during 3 hours, followed by a mixture of 75 ml. of rectified spirit and 75 ml. of water during 1 hour, and 150 ml. of water during 15 minutes. The mixture (three layers) was refluxed for 3 hours (to decompose any unchanged bromide), diluted with a large excess of water, and the hydrocarbon layer (20 g.; 32 ml.) separated. This was washed with a little water, dried with anhydrous magnesium sulphate, and distilled from sodium in a Claisen flask with a fractionating side arm, the fraction of b. p. 68·5—70° (18 g.) being collected separately. The crude *n*-hexane was washed with 3-ml. portions of concentrated sulphuric acid until the acid remained colourless (16 washings), then successively with water, 10% sodium carbonate solution and water, and finally dried with anhydrous magnesium sulphate. It was then distilled from sodium and passed over constantly at 68·7°/769 mm. : a middle fraction was used for the physical measurements. B. p. 68·7°/769 mm.; $M$ 86·17; $n_C$ 1·37313, $n_D$ 1·37505, $n_F$ 1·37958, $n_G$ 1·38268; $R_C$ 29·79, $R_D$ 29·93, $R_F$ 30·25, $R_G$ 30·47. The refractive indices at 25° were $n_C$ 1·37048, $n_D$ 1·37234, $n_F$ 1·37687, $n_G$ 1·37997; $R_C$ 29·80, $R_D$ 29·93, $R_F$ 30·26, $R_G$ 30·48. Densities determined : $d_{4^\circ}^{20^\circ}$ 0·6592, $d_{4^\circ}^{25\cdot0^\circ}$ 0·6548, $d_{4^\circ}^{42\cdot4^\circ}$ 0·6394. Apparatus *A*.

| *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | *γ*. | *P*. | *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | *γ*. | *P*. |
|---|---|---|---|---|---|---|---|---|---|
| 18·5° | 15·01 | 0·6606 | 18·57 | 271·1 | 41·4° | 13·56 | 0·6403 | 16·26 | 270·7 |
| 22·5 | 14·74 | 0·6570 | 18·13 | 271·0 | | | | Mean | 270·9 |

*Method* 2. A Grignard reagent was prepared from 12·0 g. of magnesium, 100 ml. of sodium-dried ether and a crystal of iodine contained in a 1-litre three-necked flask equipped with a separatory funnel (with guard tube), a mercury-sealed mechanical stirrer, and a long double-surface condenser (with guard tube). The separatory funnel was charged with a solution of 72·5 g. of dry *n*-hexyl bromide (VIII, **78**) in 200 ml. of anhydrous ether, and 10 g. of dry *n*-hexyl bromide were added through the condenser. The reaction started upon warming gently, and the solution of the bromide in ether was added at such a rate (*ca.* 2 hours) that the reaction was under control. The mixture was then gently refluxed, with stirring, for 2 hours, by which time most of the magnesium had reacted. The resulting solution of the Grignard reagent was then slowly added from a tap funnel into vigorously stirred ice water. The ethereal solution was separated, washed with water, saturated sodium bicarbonate solution, and water, dried (anhydrous magnesium sulphate), and distilled through a four-section Pyrex Young and Thomas column; 15 g. of crude *n*-hexane, b. p. 67—69°, were obtained. This was washed with concentrated sulphuric acid, etc., as in Method 1. B. p. 68·5°/755 mm.; $n_C$ 1·37333, $n_D$ 1·37518, $n_F$ 1·37974, $n_G$ 1·38286; $R_C$ 29·79, $R_D$ 29·92, $R_F$ 30·24, $R_G$ 30·47; $Mn_D^{20^\circ}$ 118·50. Densities determined : $d_{4^\circ}^{20^\circ}$ 0·6595, $d_D^{41\cdot3^\circ}$ 0·6399. Apparatus *A*.

| *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | *γ*. | *P*. | *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | *γ*. | *F*. |
|---|---|---|---|---|---|---|---|---|---|
| 15·4° | 15·35 | 0·6637 | 19·08 | 271·6 | 41·6° | 13·67 | 0·6396 | 16·37 | 271·5 |
| 21·1 | 14·97 | 0·6585 | 18·46 | 271·5 | | | | Mean | 271·6 |
| 23·5 | 14·88 | 0·6563 | 18·29 | 271·8 | | | | | |

* The numbering of compounds in Clarendon type follows from Part VIII (J., 1943, 639). References to compounds, the preparation of which is described in Part VIII, will be abbreviated to, *e.g.*, VIII, **50**.

† Surface-tension measurements by method of maximum bubble pressure.

Timmermans and Martin (*J. Chim. physique*, 1928, **25**, 413), for hydrocarbon from *n*-propyl bromide and sodium, give b. p. 68·80°, *d* 0·65940, $n_C$ 1·37321, $n_D$ 1·37512, $n_F$ 1·37976, $n_G$, 1·38354. Lek (Thesis, Bruxelles, 1930, p. 43) gives *d* 0·65942, *P* 270·4. Shepard *et al.* (*loc. cit.*) give b. p. 68·71°, *d* 0·65945, $n_C$ 1·37310, $n_D$ 1·37506, $n_F$ 1·37979. Mair (*loc. cit.*), for material from *n*-propyl bromide and sodium, gives b. p. 68·70°, $n_D^{25°}$ 1·37224. Wibaut *et al.* (*loc. cit.*), for hydrocarbon obtained by hydrogenation of *n*-hexene over nickel, give b. p. 68·75°, *d* 0·65943, $n_C$ 1·37300, $n_D$ 1·37499, $n_F$ 1·37950, $n_G$, 1·38325, *P* 270·7. Quayle *et al.* (*loc. cit.*) give *d* 0·6593, *P* 270·8.

**101**. n-*Heptane*. 200 G. of amalgamated zinc were prepared from 200 g. of purified zinc wool in a 2-litre three-necked flask, and the latter was equipped with an efficient double-surface condenser, a mercury-sealed mechanical stirrer, and a lead-in tube which dipped almost to the bottom of the flask and was connected through an intermediate empty wash bottle to a Kipp's apparatus generating hydrogen chloride. The amalgamated zinc was covered with a mixture of 500 ml. of concentrated hydrochloric acid and 100 ml. of water, and 80 g. of di-*n*-propyl ketone, b. p. 142·3—143·3°/758 mm. (Part V, J., 1940, 171) added. The flask was heated with a minute flame, and the mixture stirred whilst a slow stream of hydrogen chloride was passed in: the passage of gas was temporarily stopped when the reaction became too vigorous. Most of the zinc had reacted after 8 hours, and the reaction mixture was set aside overnight. It was then steam-distilled from the same flask, the organic layer (54 g.) separated, washed with water, 10% sodium carbonate solution, water, dried (anhydrous magnesium sulphate), and fractionated over sodium: the crude *n*-heptane was collected at 97—99°. This was washed repeatedly with 10% of its volume of concentrated sulphuric acid until the washings were colourless, and the pure *n*-heptane isolated as described under *n*-hexane, Method 1. B. p. 98°/763 mm.; *M* 100·20; $n_C$ 1·38564, $n_D$ 1·38758, $n_F$ 1·39231, $n_G$, 1·39572. Densities determined: $d_{4°}^{20°}$ 0·6827, $d_{4°}^{41·3°}$ 0·6661, $d_{4°}^{60·1°}$ 0·6502. Apparatus *A*.

| *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* | *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 19·5° | 16·03 | 0·6831 | 20·50 | 312·1 | 60·1° | 13·67 | 0·6502 | 16·64 | 311·7 |
| 24·2 | 15·84 | 0·6794 | 20·15 | 312·5 | | | | Mean | 312·0 |
| 41·2 | 14·69 | 0·6662 | 18·33 | 311·5 | | | | | |

Shepard *et al.* (*loc. cit.*) give b. p. 98·38°, *d* 0·68378, $n_C$ 1·38580, $n_D$ 1·38775, $n_F$ 1·39261. Mair (*loc. cit.*), for *n*-heptane from Jeffrey pine, gives b. p. 98·38°, $n_D^{25°}$ 1·38510. Wibaut *et al.* (*loc. cit.*), sample from Bureau of Standards, Washington, give b. p. 98·40°, *d* 0·68378, $n_C$ 1·38573, $n_D$ 1·38775, $n_F$ 1·39247, $n_G$, 1·39637, *P* 310·8. Quayle *et al.* (*loc. cit.*) give *d* 0·6837, *P* 311·4.

**102**. n-*Octane*. *Method* 1. The crude *n*-octane, b. p. 122—125° (30 g.), was prepared from 46 g. of sodium and 137 g. of *n*-butyl bromide (VIII, **71**)—see method under *n*-hexane. Upon purification by treatment with 10% of its volume of concentrated sulphuric acid until the acid remained colourless, etc., the *n*-octane boiled at 124·5°/760 mm. B. p. 124·5°/760 mm.; *M* 114·22; $n_C$ 1·39544, $n_D$ 1·39743, $n_F$ 1·40227, $n_G$, 1·40576. Densities determined: $d_{4°}^{20°}$ 0·7028, $d_{4°}^{40·9°}$ 0·6861, $d_{4°}^{61·1°}$ 0·6700, $d_{4°}^{84·9°}$ 0·6497. Apparatus *A*.

| *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* | *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 22·9° | 16·26 | 0·7004 | 21·32 | 350·4 | 60·3° | 14·27 | 0·6706 | 17·92 | 350·7 |
| 23·5 | 16·22 | 0·6999 | 21·26 | 350·4 | 86·0 | 12·83 | 0·6488 | 15·59 | 350·3 |
| 40·7 | 15·30 | 0·6863 | 19·66 | 350·5 | | | | Mean | 350·5 |

*Method* 2. By the Clemmensen reduction of commercial methyl *n*-hexyl ketone, b. p. 171—172° (for details, see under **101**). The *n*-octane had b. p. 125·5°/771 mm., *d* 0·7022, $n_D$ 1·39778, *P* 351·7. Timmermans and Martin, *loc. cit.*, for octane from *n*-butyl bromide and sodium, give b. p. 125·80°, *d* 0·70197, $n_C$ 1·39512, $n_D$ 1·39727, $n_F$ 1·40240. Lek (*loc. cit.*) gives *d* 0·70232, *P* 350·3. Shepard *et al.* (*loc. cit.*) give b. p. 125·59°, *d* 0·70279, $n_C$ 1·39557, $n_D$ 1·39760, $n_F$ 1·40255. Mair (*loc. cit.*), for octane from *n*-butyl bromide and sodium, gives b. p. 125·59°, $n_D^{25°}$ 1·39509. Wibaut *et al.* (*loc. cit.*), for octane obtained by hydrogenation of octene over nickel, give b. p. 125·75°, *d* 0·70280, $n_C$ 1·39562, $n_D$ 1·39770, $n_F$ 1·40252, $n_G$, 1·40648, *P* 350·6. Quayle *et al.* (*loc. cit.*) give *d* 0·7027, *P* 351·1.

**103**. n-*Nonane*. This was obtained by the Clemmensen reduction (for details, see under *n*-heptane) of methyl *n*-heptyl ketone, b. p. 192—193°/749 mm.; the latter was prepared by passage of a mixture of 3 mols. of glacial acetic and 1 mol. of *n*-octoic acid (b. p. 235—239°/760 mm.; Deutsche Hydrierwerke) over thoria at 400—450°. 96 G. of the ketone yielded 63 g. of crude *n*-nonane, b. p. 147—152° (largely 148—150°). After being shaken 18 times with 5-ml. portions of concentrated sulphuric acid, the pure *n*-nonane was isolated in the usual manner. B. p. 150·5°/759 mm.; *M* 128·25; $n_C$ 1·40339, $n_D$ 1·40543, $n_F$ 1·41041, $n_G$, 1·41420. Densities determined: $d_{4°}^{20°}$ 0·7174, $d_{4°}^{41·5°}$ 0·7015, $d_{4°}^{61·8°}$ 0·6858, $d_{4°}^{85·6°}$ 0·6672. Apparatus *D*.

| *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* | *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 17·4° | 12·99 | 0·7194 | 23·02 | 391·6 | 61·2° | 11·19 | 0·6863 | 18·97 | 390·9 |
| 20·6 | 12·88 | 0·7169 | 22·80 | 390·9 | 87·7 | 10·14 | 0·6656 | 16·67 | 389·3 |
| 26·3 | 12·66 | 0·7126 | 22·28 | 391·0 | | | | Mean | 390·7 |
| 41·4 | 12·00 | 0·7016 | 20·79 | 390·3 | | | | | |

Shepard *et al.* (*loc. cit.*) give b. p. 150·71°, *d* 0·71780, $n_C$ 1·40356, $n_D$ 1·40563, $n_F$ 1·41077. Mair (*loc. cit.*), for nonane from *n*-nonylmagnesium bromide *ex n*-heptyl bromide and ethylene oxide, gives b. p. 150·72°, $n_D^{25°}$ 1·40340. Wibaut *et al.* (*loc. cit.*), for nonane obtained by hydrogenation of nonene over nickel, give b. p. 150·70°, *d* 0·71808, $n_C$ 1·40353, $n_D$ 1·40561, $n_F$ 1·41058, $n_G$, 1·41462, *P* 390·5. Quayle *et al.* (*loc. cit.*) give *d* 0·7175, *P* 391·1.

**104**. n-*Decane*. The crude *n*-decane, b. p. 171—179° (mainly 173—175°) (45 g.), was prepared from 46 g. of sodium and 151 g. of *n*-amyl bromide (VIII, **74**)—for method see under *n*-hexane. After 19 washings with 5-ml. portions of concentrated sulphuric acid, the latter remained colourless, and the pure *n*-decane was isolated in the usual manner. B. p. 172·5°/762 mm.; *M* 142·28; $n_C$ 1·40999, $n_D$ 1·41206, $n_F$ 1·41715, $n_G$, 1·42080. Densities determined: $d_{4°}^{20°}$ 0·7301, $d_{4°}^{40·5°}$ 0·7159, $d_{4°}^{61·0°}$ 0·7007, $d_{4°}^{86·3°}$ 0·6812. Apparatus *A*.

| *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* | *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 17·1° | 17·56 | 0·7322 | 24·08 | 430·4 | 60·8° | 15·28 | 0·7006 | 20·05 | 429·7 |
| 19·0 | 17·42 | 0·7308 | 23·84 | 430·2 | 87·8 | 13·90 | 0·6801 | 17·70 | 429·1 |
| 22·3 | 17·21 | 0·7284 | 23·47 | 429·9 | | | | Mean | 429·9 |
| 41·4 | 16·35 | 0·7153 | 21·90 | 430·3 | | | | | |

Lek (*loc. cit.*) gives *d* 0·73064, *P* 429·7. Shepard *et al.* (*loc. cit.*) give b. p. 174·06°, *d* 0·73014, $n_C$ 1·40994, $n_D$ 1·41203, $n_F$ 1·41728. Mair (*loc. cit.*), for decane obtained by addition of sodium to *n*-amyl bromide, gives b. p. 174·02°, $n_D^{25°}$ 1·40961. Quayle *et al.* (*loc. cit.*) give *d* 0·7295, *P* 431·3.

**105.** n-*Undecane.* This hydrocarbon was obtained by Clemmensen reduction of di-*n*-amyl ketone, b. p. 222—224° (prepared by passing *n*-hexoic acid over thoria at 400—450°). 100 G. of the ketone yielded 82 g. of distillate (for details, see under *n*-heptane). This contained an appreciable quantity of di-*n*-amylcarbinol; distillation gave a fraction of b. p. 195—220° (75 g.). The secondary alcohol was removed as the non-volatile sodium compound by refluxing it for several hours over, and then distilling it from, a large excess of sodium; this treatment gave 41 g. of crude *n*-undecane, b. p. 185—195°, or 190—194° upon redistillation. The crude hydrocarbon was treated with concentrated sulphuric acid until the acid layer was colourless (17 washings with 4-ml. portions of concentrated sulphuric acid were required), water, 10% sodium carbonate solution, water, and dried over anhydrous magnesium sulphate. The last traces of moisture were removed by standing over sodium for several hours, and the hydrocarbon was twice distilled under reduced pressure; there is slight decomposition at atmospheric pressure. B. p. 87°/20 mm.; *M* 156·30; $n_C$ 1·41507, $n_D$ 1·41716, $n_F$ 1·42229, $n_G$ 1·42603. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·7398, $d_{4^\circ}^{41\cdot1^\circ}$ 0·7252, $d_{4^\circ}^{60\cdot8^\circ}$ 0·7108, $d_{4^\circ}^{87\cdot1^\circ}$ 0·6913. Apparatus *A*.

| *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | *P.* | *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 26·3° | 17·47 | 0·7353 | 24·05 | 470·7 | 62·1° | 15·73 | 0·7099 | 20·19 | 470·8 |
| 28·1 | 17·38 | 0·7340 | 23·89 | 470·8 | 87·2 | 14·46 | 0·6912 | 18·72 | 470·3 |
| 40·8 | 16·74 | 0·7254 | 22·73 | 470·5 | | | | Mean | 470·6 |

Shepard *et al.* (*loc. cit.*) give b. p. 195·84°, *d* 0·74025, $n_C$ 1·41514, $n_D$ 1·41727, $n_F$ 1·42252. Mair (*loc. cit.*), for undecane from undecylene and hydrogen over copper chromite catalyst, gives $n_D^{25^\circ}$ 1·41495. Quayle *et al.* (*loc. cit.*) gives *d* 0·7406, *P* 470·8.

**106.** n-*Dodecane.* The crude product (75 g.) produced by the action of 165 g. of *n*-hexyl bromide (VIII, **78**) upon 46 g. of sodium (for method, see under *n*-hexane) was washed with 5-ml. portions of concentrated sulphuric acid until the acid layer was colourless (16 washings), water, 10% sodium carbonate solution, water, and dried over anhydrous magnesium sulphate, followed by sodium. The hydrocarbon was then distilled twice under diminished pressure. B. p. 94°/13·5 mm.; *M* 170·33; $n_C$ 1·41967, $n_D$ 1·42186, $n_F$ 1·42697, $n_G$ 1·43068. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·7498, $d_{4^\circ}^{41\cdot0^\circ}$ 0·7348, $d_{4^\circ}^{61\cdot5^\circ}$ 0·7204, $d_{4^\circ}^{85\cdot7^\circ}$ 0·7026. Apparatus *D*.

| *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | *P.* | *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 14·5° | 13·86 | 0·7537 | 25·80 | 509·3 | 63·0° | 12·13 | 0·7193 | 21·55 | 510·2 |
| 18·5 | 13·78 | 0·7509 | 25·55 | 510·2 | 86·5 | 11·26 | 0·7020 | 19·52 | 510·0 |
| 22·5 | 13·72 | 0·7480 | 25·34 | 510·9 | | | | Mean | 510·0 |
| 41·5 | 12·86 | 0·7344 | 23·32 | 509·7 | | | | | |

Shepard *et al.* (*loc. cit.*) give b. p. 216·23°, $d_{4^\circ}^{25^\circ}$ 0·74542, $n_C$ 1·41965, $n_D$ 1·42188, $n_F$ 1·42720. Mair (*loc. cit.*), for dodecane from sodium and *n*-hexyl bromide, gives $n_D^{25^\circ}$ 1·41967.

**107.** n-*Tridecane.* Clemmensen reduction of 78 g. of di-*n*-hexyl ketone, m. p. 32°, b. p. 117·5°/7 mm. (prepared by passing redistilled *n*-heptoic acid over thoria at 400—450°) yielded 74 g. of steam-volatile products (for details, see under *n*-heptane) consisting largely of *n*-tridecane and di-*n*-hexylcarbinol. The latter was converted into the sodium derivative by heating with a large excess of sodium at 150—160°, and, after cooling, this was filtered off and washed with a little sodium-dried ether. The filtrate was distilled under reduced pressure and 45 g. of crude *n*-tridecane, b.p. 99—100°/7 mm., were obtained. After treatment with 4-ml. portions of concentrated sulphuric acid until the acid layer was colourless (18 washings), the pure *n*-tridecane was isolated as described under *n*-undecane. B. p. 92·5°/4·5 mm.; *M* 184·35; $n_C$ 1·42326, $n_D$ 1·42541, $n_F$ 1·43068, $n_G$ 1·43438. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·7559, $d_{4^\circ}^{41\cdot0^\circ}$ 0·7414, $d_{4^\circ}^{60\cdot4^\circ}$ 0·7289, $d_{4^\circ}^{85\cdot7^\circ}$ 0·7110. Apparatus *A*.

| *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | *P.* | *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 21·3° | 18·30 | 0·7550 | 25·87 | 550·7 | 87·7° | 15·15 | 0·7097 | 20·13 | 550·2 |
| 41·1 | 17·35 | 0·7419 | 24·10 | 550·6 | | | | Mean | 550·5 |
| 61·9 | 16·36 | 0·7279 | 22·30 | 550·4 | | | | | |

**108.** n-*Tetradecane.* 27·5 G. of clean sodium were allowed to react with 107 g. of *n*-heptyl bromide (VIII, **79**), the procedure described under *n*-hexane being followed. The mixture was then treated with 120 ml. of rectified spirit (90 minutes), 60 ml. of 50% alcohol (30 minutes), and 60 ml. of water (10 minutes), the whole (three layers) refluxed for 3 hours, allowed to cool, and then poured into a large excess of water. The hydrocarbon layer (52·5 g.) was then shaken with 5-ml. portions of concentrated sulphuric acid until the acid remained colourless (16 washings), washed with water 10% sodium carbonate solution, and water, and dried with anhydrous magnesium sulphate and then with sodium. The *n*-tetradecane (44 g.) was twice distilled under diminished pressure—the first distillation removes high-boiling impurities.* B. p. 123°/12 mm.; *M* 198·38; $n_C$ 1·42688, $n_D$ 1·42907, $n_F$ 1·43433, $n_G$ 1·43818. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·7624, $d_{4^\circ}^{40\cdot6^\circ}$ 0·7494, $d_{4^\circ}^{61\cdot5^\circ}$ 0·7348, $d_{4^\circ}^{86\cdot3^\circ}$ 0·7175. Apparatus *D*.

| *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | *P.* | *t.* | *H.* | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 21·5° | 14·11 | 0·7614 | 26·53 | 591·3 | 60·2° | 12·74 | 0·7357 | 23·15 | 591·5 |
| 25·2 | 13·96 | 0·7589 | 26·16 | 591·2 | 87·8 | 11·78 | 0·7165 | 20·84 | 591·6 |
| 40·0 | 13·46 | 0·7492 | 24·90 | 591·5 | | | | Mean | 591·4 |

**109.** n-*Pentadecane.* 58·5 G. of di-*n*-heptyl ketone, m. p. 43°, b. p. 139·5°/5 mm. [prepared by passing *n*-octoic acid, b. p. 235—239° (Deutsche Hydrierwerke) over thoria at 400—450°], was reduced with 200 g. of amalgamated zinc (for details, see under *n*-heptane). After 24 hours, the organic layer (52 g.) was separated from the reaction mixture, and washed successively with water, 10% sodium carbonate solution, and water, and then dried over anhydrous magnesium sulphate. It was then heated with a large excess of sodium at 120—130° for 6 hours, the resulting sodium derivative of di-*n*-heptylcarbinol filtered off on a sintered-glass funnel, and washed with a little sodium-dried ether. The filtrate was distilled under reduced pressure and 30 g. of crude *n*-pentadecane, b. p. 112—116°/3·3—3·7 mm., were obtained. This was shaken with 4-ml. portions of concentrated sulphuric acid until the acid layer was colourless (25 washings), and the pure hydrocarbon isolated as under *n*-undecane. B. p. 120°/4·5 mm.; *M* 212·41; $n_C$ 1·42980, $n_D$

* It is noteworthy that Bachmann and Clarke (*J. Amer. Chem. Soc.*, 1927, **49**, 4097), by treating 1074 g. of *n*-heptyl bromide, heated to 150° and vigorously stirred, with 100 g. of sodium, followed by adding water, isolating the oil and again treating the latter with sodium until no further action took place, obtained yields of 9% of *n*-heptane, b. p. 96—99°, 3% of heptylene, 67% of *n*-tetradecane, b. p. 115—117°/10 mm., m. p. 4—4·5°, 3% of heneicosane, b. p. 340—345°, and hydrocarbons of higher molecular weight.

1·43199, $n_F$ 1·43734, $n_G$ 1·44126. Densities determined: $d_4^{20°}$ 0·7687, $d_4^{41·0°}$ 0·7549, $d_4^{61·4°}$ 0·7412, $d_4^{86·7°}$ 0·7236. Apparatus *A*.

| *t.* | *H.* | $d_4^{t°}$. | γ. | *P.* | *t.* | *H.* | $d_4^{t°}$. | γ. | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 22·6° | 18·78 | 0·7670 | 26·97 | 631·1 | 86·0° | 15·97 | 0·7241 | 21·65 | 631·1 |
| 40·9 | 17·97 | 0·7550 | 25·43 | 631·1 | | | | Mean | 631·3 |
| 62·0 | 16·99 | 0·7408 | 23·57 | 631·8 | | | | | |

**110**. n-*Hexadecane*. Interaction of 31 g. of sodium and 129 g. of *n*-octyl bromide, b. p. 199—200°/764 mm. (VIII, **80**), as described under *n*-hexane gave 73 g. of the crude hydrocarbon. After 20 washings with 6-ml. portions of concentrated sulphuric acid,* the acid layer still had a deep yellow colour; the residual hydrocarbon was accordingly washed with water, 10% sodium carbonate solution, water, dried over anhydrous magnesium sulphate (weight dry, 54 g.), and distilled. The crude *n*-hexadecane (32 g.) was collected at 146—150°/11 mm. and a considerable dark residue remained. After three washings with 3-ml. portions of concentrated sulphuric acid, the acid remained colourless: the *n*-hexadecane, which was isolated in the usual manner, distilled at a constant temperature. B. p. 143·5°/9 mm., m. p. 18°; *M* 226·43; $n_C$ 1·43241, $n_D$ 1·43465, $n_F$ 1·44004, $n_G$ 1·44391. Densities determined: $d_4^{20°}$ 0·7743, $d_4^{41·0°}$ 0·7598, $d_4^{61·1°}$ 0·7464, $d_4^{86·9°}$ 0·7291. Apparatus *A*.

| *t.* | *H.* | $d_4^{t°}$. | γ. | *P.* | *t.* | *H.* | $d_4^{t°}$. | γ. | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 21·1° | 19·00 | 0·7735 | 27·52 | 670·6 | 62·1° | 17·16 | 0·7457 | 23·96 | 671·8 |
| 27·4 | 18·77 | 0·7693 | 27·04 | 671·2 | 87·5 | 16·04 | 0·7287 | 21·89 | 672·1 |
| 41·4 | 18·08 | 0·7595 | 25·71 | 671·0 | | | | Mean | 671·3 |

Wibaut *et al.* (*loc. cit.*), for hexadecane obtained by hydrogenation of cetene over nickel, give m. p. 17·9°, *d* 0·77387, $n_C$ 1·43242, $n_D$ 1·43470, $n_F$ 1·44022, $n_G$ 1·44451.

**111**. 2 : 6-*Dimethylheptane* (*diisobutylmethane*). 60 G. of redistilled di*iso*butyl ketone, b. p. 164—166°/753 mm. (General and Metallurgical; Carbon and Carbide Corporation) was reduced by 200 g. of amalgamated zinc (for details, see under *n*-heptane). The steam distillate was washed with water, saturated sodium bicarbonate solution, water, dried, and distilled; the fraction, b. p. 138—155°, was collected. This contained some di*iso*butylcarbinol, which was removed by refluxing it for 3 hours with a large excess of sodium, allowing it to stand overnight, and distilling it; 12 g. of crude di*iso*butylmethane, b. p. 131—134° (mainly 133—134°), were obtained. The crude hydrocarbon was purified by shaking with 1-ml. portions of concentrated sulphuric acid until the acid remained colourless (14 washings), etc. B. p. 134·5°/761 mm.; *M* 128·25; $n_C$ 1·39872, $n_D$ 1·40077, $n_F$ 1·40574, $n_G$ 1·40936. Densities determined: $d_4^{20°}$ 0·7098, $d_4^{42·1°}$ 0·6921, $d_4^{61·0°}$ 0·6773, $d_4^{84·6°}$ 0·6576. Apparatus *A*.

| *t.* | *H.* | $d_4^{t°}$. | γ. | *P.* | *t.* | *H.* | $d_4^{t°}$. | γ. | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 12·9° | 16·18 | 0·7155 | 21·68 | 386·8 | 63·0° | 13·47 | 0·6757 | 17·04 | 385·7 |
| 18·8 | 15·86 | 0·7108 | 21·11 | 386·7 | 86·8 | 12·37 | 0·6558 | 15·19 | 386·1 |
| 22·7 | 15·68 | 0·7076 | 20·78 | 387·0 | | | | Mean | 386·5 |
| 42·9 | 14·58 | 0·6915 | 18·88 | 386·6 | | | | | |

**112**. 2 : 5-*Dimethylhexane* (*diisobutyl*). This was prepared in the usual manner (see under *n*-hexane) from 46 g. of sodium and 137 g. of *iso*butyl bromide (VIII, **72**A). When all the bromide had been introduced, the flask was well shaken, whereupon a vigorous reaction set in and the liquid refluxed in the condenser. After 15—20 minutes, the flask was shaken again, etc.; the shaking and standing were repeated until no visible reaction occurred upon shaking After 2 hours, the excess of sodium was decomposed as before, the liquid mixture refluxed for 4 hours, and allowed to stand overnight. Dilution with excess of water gave 48 g. of the crude hydrocarbon. This was purified by shaking with concentrated sulphuric acid until the acid remained colourless (10 3-ml. portions). The yield of pure di*iso*butyl was 43 g. B. p. 109°/760 mm.; *M* 114·22; $n_C$ 1·39069, $n_D$ 1·39270, $n_F$ 1·39756, $n_G$ 1·40099. Densities determined: $d_4^{20°}$ 0·6942, $d_4^{41·1°}$ 0·6759, $d_4^{61·6°}$ 0·6586, $d_4^{85·3°}$ 0·6379. Apparatus *A*.

| *t.* | *H.* | $d_4^{t°}$. | γ. | *P.* | *t.* | *H.* | $d_4^{t°}$. | γ. | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 15·1° | 15·48 | 0·6984 | 20·24 | 346·9 | 61·1° | 13·03 | 0·6583 | 16·06 | 347·8 |
| 23·8 | 15·13 | 0·6909 | 19·57 | 347·7 | 83·0 | 11·79 | 0·6399 | 14·13 | 347·0 |
| 40·9 | 14·21 | 0·6761 | 17·99 | 347·9 | | | | Mean | 347·5 |

Wibaut *et al.* (*loc. cit.*), for hydrocarbon obtained by electrolysis of potassium *iso*valerate with a platinum anode, give b. p. 109·25°, *d* 0·69426, $n_C$ 1·39081, $n_D$ 1·39285, $n_F$ 1·39772, $n_G$ 1·40169, *P* 346·8.

**113**. 3 : 4-*Dimethylhexane* (*di*-sec.-*butyl*). To 46 g. of sodium, contained in a 1-litre round-bottomed flask equipped with two 25-cm. double-surface condensers in series, was added about one-quarter of the total quantity (137 g.) of dry *sec.*-butyl bromide (VIII, **73**). The mixture was gently heated under reflux for 1 hour, but little action occurred apart from the formation of a few blue spots upon the sodium. Reaction was initiated by addition of 3 ml. of rectified spirit; the whole surface of the sodium then acquired a blue colour. The remainder of the *sec.*-butyl bromide was added in two equal quantities during 1 hour with frequent shaking. A further 4 ml. of rectified spirit was added, the mixture refluxed for 1 hour, and the process repeated. Upon allowing the mixture to cool somewhat and shaking it vigorously, a lively reaction set in, resulting in the formation of molten sodium and some unsaturated hydrocarbon (probably butene). Further shaking had little effect, but the dropwise addition of 10 ml. of rectified spirit produced a renewed vigorous reaction. After standing overnight, the excess of sodium was decomposed in the usual manner by addition of 100 ml. of rectified spirit (90 minutes), 100 ml. of 50% alcohol (45 minutes), and 150 ml. of water (15 minutes). The mixture was refluxed for 6 hours to hydrolyse any unchanged bromide, poured into a large excess of water, and, after filtering from a little tarry matter, the crude hydrocarbon (9 g.) was separated. Repetition of the above experiment but with ethyl acetate (in 1-ml. portions) as catalyst gave 7 g. of the crude hydrocarbon. The combined products were shaken with 1-ml. portions of concentrated sulphuric acid until the acid layer was colourless (17 washings) and the hydrocarbon was isolated in the usual manner and fractionated twice from sodium. B. p. 117°/758 mm.; *M* 114·22; $n_C$ 1·40242, $n_D$ 1·40445, $n_F$ 1·40933, $n_G$ 1·41289. Densities determined: $d_4^{20°}$ 0·7200, $d_4^{41·7°}$ 0·7033, $d_4^{61·6°}$ 0·6871, $d_4^{86·4°}$ 0·6662. Apparatus *A*

| *t.* | *H.* | $d_4^{t°}$. | γ. | *P.* | *t.* | *H.* | $d_4^{t°}$. | γ. | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 21·2° | 16·13 | 0·7190 | 21·72 | 342·9 | 61·9° | 13·84 | 0·6869 | 17·80 | 341·9 |
| 41·8 | 14·98 | 0·7032 | 19·72 | 342·3 | 86·6 | 12·57 | 0·6660 | 15·68 | 342·0 |
| | | | | | | | | Mean | 342·3 |

* The number of washings with concentrated sulphuric acid would probably be considerably reduced if the crude hydrocarbon were first subjected to a preliminary distillation to remove low- and high-boiling impurities.

Wibaut *et al.* (*loc. cit.*), for hydrocarbon from " molecular " sodium and *sec.*-butyl bromide in ethereal solution, give b. p. 117·85°, *d* 0·71951, $n_C$ 1·40224, $n_D$ 1·40436, $n_F$ 1·40924, $n_G$ 1·41323, *P* 342·4.

**114**. 2 : 7-*Dimethyloctane* (*di*isoamyl, " synthetic "). The reaction between 46 g. of sodium and 151 g. of *iso*amyl bromide (VIII, **75**A, from Sharples's synthetic *iso*amyl alcohol) (for details, see under *n*-hexane) yielded, after refluxing the solution for 6 hours, 48 g. of dry crude hydrocarbon. The crude di*iso*amyl, b. p. 155—163° (mainly 159—161°) (36 g.) was separated by fractionation, and then shaken with 3-ml. portions of concentrated sulphuric acid until the acid layer remained colourless (10 washings), etc. The yield of pure 2 : 7-dimethyloctane was 34 g. B. p. 160—161°/773 mm.; *M* 142·28; $n_C$ 1·40786, $n_D$ 1·40994, $n_F$ 1·41501, $n_G$ 1·41867. Densities determined : $d_4^{20°}$ 0·7283, $d_4^{41·3°}$ 0·7119, $d_4^{61·7°}$ 0·6963, $d_4^{86·9°}$ 0·6766. Apparatus *A*.

| *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* | *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 14·0° | 16·79 | 0·7329 | 23·04 | 425·3 | 62·1° | 14·31 | 0·6960 | 18·65 | 424·4 |
| 16·3 | 16·69 | 0·7311 | 22·85 | 425·5 | 87·3 | 13·05 | 0·6763 | 16·53 | 424·2 |
| 41·4 | 15·41 | 0·7118 | 20·54 | 425·5 | | | | Mean | 425·1 |

Von Auwers and Eisenlohr (*Z. physikal. Chem.*, 1913, **83**, 430) give b. p. 158·0—159·5°/760 mm., $d_4^{18·1°}$ 0·7278, $n_C^{18·1°}$ 1·40715, $n_F^{18·1°}$ 1·41435, $n_G^{18·1°}$ 1·41854.

**114**A. 2 : 7-*Dimethyloctane* (*di*isoamyl, " fermentation "). The reaction between 46 g. of sodium and 151 g. of *iso*amyl bromide (VIII, **75**, from Bisol " fermentation " *iso*amyl alcohol) gave 52 g. of the crude hydrocarbon, which was treated as under **114**. B. p. 160·5°/773 mm.; $n_C$ 1·40647, $n_D$ 1·40855, $n_F$ 1·41363, $n_G$ 1·41717. Densities determined : $d_4^{20°}$ 0·7237, $d_4^{41·1°}$ 0·7084, $d_4^{59·2°}$ 0·6947, $d_4^{86·0°}$ 0·6740. Apparatus *A*.

| *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* | *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 13·0° | 16·76 | 0·7289 | 22·87 | 426·9 | 62·1° | 14·30 | 0·6926 | 18·55 | 426·3 |
| 24·2 | 16·35 | 0·7206 | 21·56 | 425·5 | 86·1 | 13·03 | 0·6739 | 16·44 | 425·1 |
| 41·6 | 15·29 | 0·7080 | 20·27 | 426·4 | | | | Mean | 426·1 |

Lek (*loc. cit.*) gives *d* 0·72257, *P* 426·9.

**115**. 4 : 5-*Dimethyloctane*. The reaction between 46 g. of sodium and 151 g. of 2-bromopentane (VIII, **76**) proceeded similarly to that already described under di-*sec.*-butyl, and 3 ml. of anhydrous ethyl acetate (catalyst) were added in several portions. Some pentene was formed and the yield of purified 4 : 5-*dimethyloctane* (Found : C, 84·5; H, 15·6. $C_{10}H_{22}$ requires C, 84·4; H, 15·6%) was 10 g. B. p. 159—160°/769 mm.; *M* 142·28; $n_C$ 1·41517, $n_D$ 1·41726, $n_F$ 1·42233, $n_G$ 1·42595. Densities determined : $d_4^{20°}$ 0·7458, $d_4^{41·9°}$ 0·7304, $d_4^{62·2°}$ 0·7148, $d_4^{86·0°}$ 0·6964. Apparatus *D*.

| *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* | *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 21·5° | 12·66 | 0·7447 | 23·28 | 419·7 | 60·0° | 11·22 | 0·7164 | 19·85 | 419·2 |
| 41·5 | 11·97 | 0·7307 | 21·60 | 419·8 | 86·8 | 10·24 | 0·6958 | 17·60 | 418·8 |
| | | | | | | | | Mean | 419·4 |

**116**. 3 : 4-*Diethylhexane*. This was prepared from 59 g. of sodium and 258 g. of 3-bromopentane (VIII, **77**), the procedure described under di-*sec.*-butyl being followed; 5 ml. of pure ethyl acetate, added in 1-ml. portions, were employed as catalyst. Much low-boiling material (containing pentene) was produced and the yield of purified 3 : 4-*diethylhexane* (Found : C, 84·6; H, 15·6. $C_{10}H_{22}$ requires C, 84·4; H, 15·6%) was 12 g. B. p. 158·5—159·5°/764 mm.; *M* 142·28; $n_C$ 1·41687, $n_D$ 1·41896, $n_F$ 1·42401, $n_G$ 1·42769. Densities determined : $d_4^{20°}$ 0·7510, $d_4^{41·4°}$ 0·7347, $d_4^{62·4°}$ 0·7194, $d_4^{86·8°}$ 0·7005. Apparatus *D*.

| *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* | *t.* | *H.* | $d_{4°}^{t°}$. | *γ.* | *P.* |
|---|---|---|---|---|---|---|---|---|---|
| 22·0° | 12·61 | 0·7495 | 23·34 | 417·3 | 60·5° | 11·16 | 0·7211 | 19·87 | 416·6 |
| 42·3 | 11·89 | 0·7340 | 21·55 | 417·6 | 88·5 | 10·13 | 0·6992 | 17·49 | 416·2 |
| | | | | | | | | Mean | 417·0 |

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WOOLWICH POLYTECHNIC, LONDON, S.E.18. [*Received, October 5th*, 1945.]

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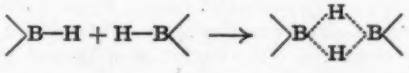
## 39. *The Structure of Some Electron-deficient Molecules.*

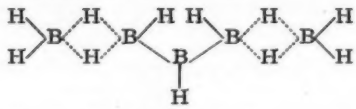
By H. C. LONGUET-HIGGINS.

In this paper the hydrogen bridge theory of diborane is extended in detail to the borohydrides and the other covalent hydrides of elements in the first three groups of the Periodic Table. In particular, the theory relates the structure and properties of all the known borohydrides to those of diborane, and accounts for the non-volatility of the newly discovered aluminium hydride $(AlH_3)_n$, for which a hexagonal layer structure is predicted. It is further shown that the theory provides possible mechanisms for the anomalous polymerisation of the alkyls of elements in the first three periodic groups.

PITZER (*J. Amer. Chem. Soc.*, 1945, **67**, 1126) has recently shown how the hydrogen bridge theory of diborane, for which strong evidence has been advanced by the author and Bell (J., 1943, 250; *Proc. Roy. Soc.*, 1945, **183**, *A*, 357), can be extended to account for the formulæ and properties of all the known hydrides of boron, and for the non-existence of any others with six or fewer boron atoms. The main essentials of this theory are : (1) That the hydroborons are all built up of smaller units, conveniently termed " borines," of general formula $B_nH_{n+2}$ and containing tervalent boron, linked together by hydrogen bridges through their free $>$B—H groups :



(2) That this polymerisation will continue until there are no free >B—H groups left, except those adjacent to two bridges, such as the central >B—H groups in $B_5H_{11}$, which is formulated as (I). (3) That hydroborons containing rings of fewer than five boron atoms are not stable.

(I.) 

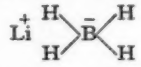
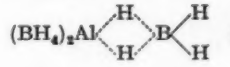
The absence of further polymerisation in $B_5H_{11}$ and similar systems is explained by Pitzer in terms of a new conception of the hydrogen-bridge linkage, as a " protonated double bond " between the boron atoms. This may be thought of as a $\sigma$ bond together with a $\pi$ bond in whose antinodes two protons are embedded. The $\pi$ parts of the protonated double bonds in $B_5H_{11}$ can conjugate through the $2p$ orbital of the central boron atom, thereby preventing further polymerisation.

Not only is this theory completely successful in accounting for the formulæ of the known hydroborons, but it also explains their individual properties. In particular, Pitzer shows that the structure predicted for $B_5H_9$ agrees as well with the evidence from electron diffraction (Bauer and Pauling, *J. Amer. Chem. Soc.*, 1934, **58**, 2403) as that proposed by Bauer and Pauling, with reasonable values for the dimensions of the molecule. It is also noteworthy that the two series of hydroborons, of general formulæ $B_nH_{n+4}$ and $B_nH_{n+6}$, are simply those consisting of two and three borines respectively; and all the cyclic hydroborons, which would be expected to be more stable, belong to the former series, whereas all those in the latter series are chain molecules. Hence Stock's classification (" Hydrides of Boron and Silicon," Cornell Univ. Press, Ithaca, 1935) relating stability and formula finds a theoretical foundation.

In economy of hypothesis and in the range of experimental evidence which it explains, this theory is considerably superior to any previous theory of the boron hydrides; and since there are at present no experimental facts which conflict with it, we believe that it is substantially correct.

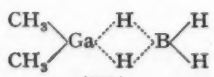
In the present paper we extend the theory to other electron-deficient molecules, *viz.*, the borohydrides (which were discussed briefly in another paper, *loc. cit.*, 1943), the other hydrides of Group III, the non-ionic hydrides of Groups I and II, and the associated alkyls of these three groups. The adjective " electron-deficient " implies the difficulty in formulating these compounds according to classical valency ideas: their molecules have insufficient valency electrons to hold them together entirely by 2-electron covalent links, whereas their properties (apart from those of $LiBH_4$) conflict with the view that they contain pure ionic links.

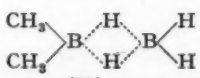
*The Borohydrides.*—It has already been suggested elsewhere (*loc. cit.*, 1943) that the borohydrides have structures resembling those of the boron hydrides in containing bridge linkages through hydrogen. It seems reasonable to suppose that in lithium borohydride the ionic structure (II) predominates, whereas in the aluminium compound a larger contribution comes from covalent structures of the type (III). This accords with the physical properties of these compounds, of which the volatility increases enormously from $LiBH_4$ to $Al(BH_4)_3$.

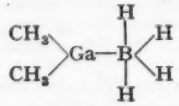
(II.)   (III.)

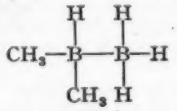
Moreover, there is chemical evidence to support this formulation. Schlesinger and Brown in their discussion (*J. Amer. Chem. Soc.*, 1940, **62**, 3429) of the borohydrides draw attention to the series of compounds $LiBH_4$, $Be(BH_4)_2$, $Al(BH_4)_3$, $B_2H_6$. Along this series there is a progressive decrease in stability towards air and water, and a progressive ease of reaction with trimethylamine to form $BH_3NMe_3$. They describe this change as an " increase of $BH_3$ character " and a " decrease of $BH_4^-$ character." This progressive change in chemical properties is obscured if we suppose (see Beach and Bauer, *ibid.*, p. 3440) beryllium and aluminium borohydrides to contain quinquevalent boron, and lithium borohydride and diborane to contain quadrivalent boron.

Another piece of evidence pointing to a continuity between the borohydrides and boranes is the recent discovery of dimethylgallium borohydride (Schlesinger, Brown, and Schaeffer, *ibid.*, 1943, **65**, 1838). According to the present theory this compound is formulated as (IV), in close relationship to the formula for 1 : 1-dimethyldiborane (V). One may contrast this scheme with that put forward by Pauling and others (see Beach


(IV.)


(V.)


(IV*a*).


(V*a*.)

and Bauer, *loc. cit.*), in which the borohydrides are supposed to contain quinquevalent boron, each link being partly ionic, partly covalent, and partly a one-electron bond. In the latter theory the borohydrides are regarded as essentially different in structure from the boranes; for instance, dimethylgallium borohydride and 1 : 1-dimethyldiborane are assigned the structures (IV*a*) and (V*a*) respectively.

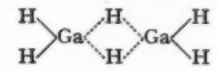
*The Covalent Hydrides of the Metals.*—For the existence of these there is now much evidence. In 1933 Pietsch (*Z. Elektrochem.*, **39**, 577) reported the formation of hydrides of Cu, Ag, Au, Be, Ga, In, Tl and Ta by the action of atomic hydrogen on the elements. The hydrides of In and Tl were volatile, but the others were

white solid films of uncertain composition, decomposing water with evolution of hydrogen. In recent years a volatile hydride of gallium (Wiberg and Johansen, *Angew. Chem.*, **1942**, **55**, 38) and a non-volatile hydride of aluminium (Stecher and Wiberg, *Ber.*, **1942**, **75**, 2003) have been discovered, and also methylaluminium hydrides (*idem*, *ibid.*) of general formula $Al_2Me_nH_{6-n}$.

Pietsch regarded his " atomic hydrides " as containing metallic cations and hydrogen anions, but in view of the relative electronegativities of these metals and hydrogen this description is inacceptable. However, the non-volatility of the hydrides of Cu, Ag, Au, Be and Ta indicates that they are not covalent separate molecules but polymers. In aluminium hydride, where there are definitely three hydrogen atoms to each aluminium atom, it is therefore impossible to formulate the molecule according to classical valency ideas.

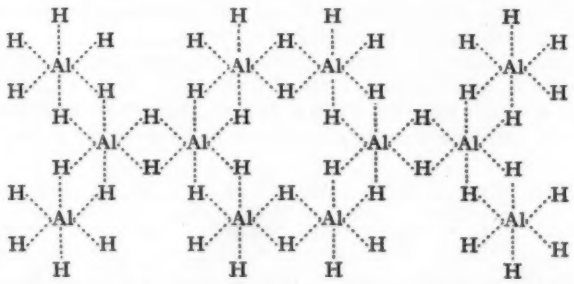
The present theory provides a satisfactory solution to the problem. It has already been suggested (*loc. cit.*, 1943) that the volatile $Ga_2H_6$ has the structure (VI) analogous to that of $B_2H_6$, and it seems likely that the

(VI.)

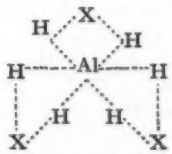



volatile hydrides of In and Tl have similar structures. As regards aluminium hydride $(AlH_3)_n$, we suppose that the unit >Al—H can polymerise like >B—H, but that whereas the polymerisation of the latter stops when the boron atom has its four valency shell orbitals occupied, the polymerisation of the former will continue until six of its valency orbitals are occupied. This is an extension of the idea of a " covalency maximum " to these anomalous compounds, and has already been tacitly assumed in our formulation of $Al(BH_4)_3$. The monomeric $AlH_3$ could then polymerise in two dimensions by the continued formation of bridge linkages as in (VII).

(VII.)

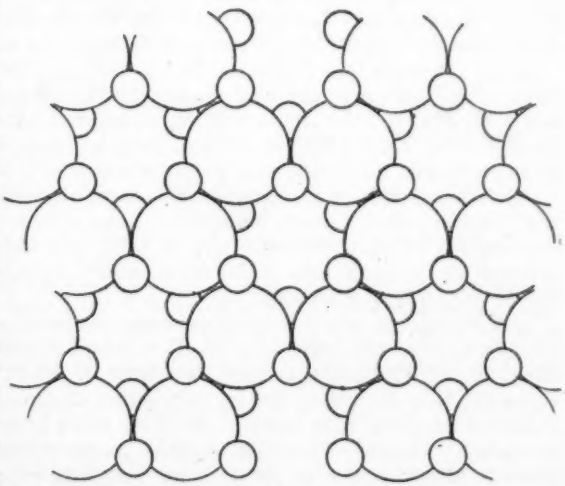


(VIII.)




In fact, if we assume that (*a*) the hydrogen atoms form bridges in pairs between the Al atoms, every Al atom being joined octahedrally to six H atoms, and (*b*) all the Al····H bonds in the giant molecule are crystallographically equivalent, then it follows that the Al atoms must be arranged in two-dimensional layers, with the Al atoms in each layer at the vertices of a hexagonal tessellation. One such layer is illustrated in Fig. 1, where the large circles represent Al atoms and the small circles H atoms. However, if we accept Pitzer's view (*loc. cit.*) of the hydrogen bridge as a " protonated double bond," it seems likely that the hydrogen atoms in the group (VIII) may be arranged, not at the vertices of an octahedron, but at the vertices of a trigonal prism with the aluminium atom at the centre. The Al–X $\sigma$ orbitals can be constructed from a linear combination of $3s$, $3p_x$, and $3p_y$ orbitals ($z$ axis perpendicular to the plane of the heavy atoms); and of the remaining orbitals, $3p_z$, $3d_{xy}$, and $3d_{zz}$ can be combined linearly to give three $\pi$ orbitals directed towards the three X atoms and having nodal planes $z = 0$. The protons would be situated near the antinodes of these $\pi$ bonds, that is, at the vertices of a trigonal prism (Fig. 2). This configuration leads to the same arrangement of the heavy atoms in $(AlH_3)_n$ and $Al(BH_4)_3$ as the octahedral configuration (Fig. 3), so it would be difficult to distinguish the two possibilities by electron-diffraction or $X$-ray analysis; a more hopeful line might be to investigate some property depending on the symmetry of the borohydride, since with the prismatic arrangement this molecule has the symmetry $D_{3h}$ with reflexive summetry, whereas with the octahedral configuration it belongs to the group $D_3$ with no reflexive symmetry.

FIG. 1.



As for the methyl derivatives of aluminium hydride, one can formulate many plausible polymers derived from the units $AlH_3$, $AlH_2Me$, $AlHMe_2$, and $AlMe_3$. Moreover, the monomeric $AlMe_3$ can polymerise on its own (see next section), which shows that the presence of Al–H bonds is not necessary for polymerisation;

this greatly increases the number of possible polymers, and makes less certain the formulation of any particular one. Generally speaking, however, this scheme is in excellent agreement with experiment: it appears (Stecher and Wiberg, *loc. cit.*) that the interconversion of the polymers takes place through the intermediate formation of such monomeric units, and the more hydrogen a polymer contains the greater its degree of polymerisation, as estimated from the volatility and viscosity.

FIG. 2.

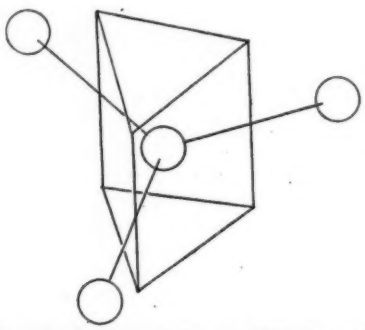
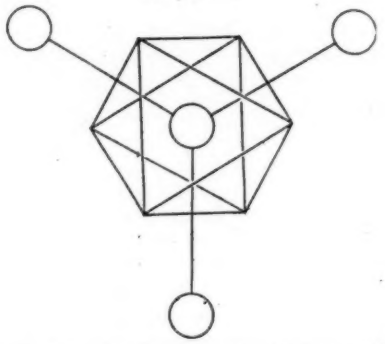
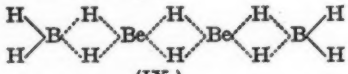


FIG. 3.

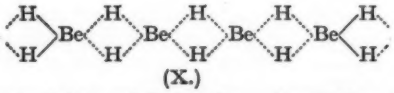


As for the other hydrides of Group III, the absence of further polymerisation in gallium, indium, and thallium hydrides is probably connected with the general reluctance of these sub-group B elements to attain a co-ordination number of six; the atomic orbitals involved would be the same.

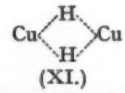
No beryllium hydride of definite composition has yet been prepared, but even apart from Pietsch's work there are indications that one exists. Burg and Schlesinger (*J. Amer. Chem. Soc.*, 1940, **62**, 3425) describe the preparation of a compound $BeBH_5$ which was left as a solid after $BeB_2H_8$ had been distilled away. This may be written as (IX). If this is correct one would naturally expect there to exist a beryllium hydride $(BeH_2)_n$ of structure (X).



(IX.)



(X.)



(XI.)

At present there is little evidence about the hydrides of Group IB. According to the present ideas a univalent hydride can polymerise only two-fold, to give a structure of the type (XI). The copper hydride formed by the action of sodium hypophosphite on cupric salts is probably not of this type, however, according to the crystal evidence (Huttig and Brodkorb, *Z. anorg. Chem.*, 1926, **153**, 242).

*The Alkyls of Elements of Groups* I, II, *and* III.—These include LiR, NaR; $BeR_2$, $MgR_2$, $ZnR_2$, $CdR_2$, $HgR_2$; $BR_3$, $AlR_3$, $GaR_3$, $InR_3$, $TlR_3$. Of these, the alkyls of Li, Na, Be, Mg and Al have the properties of associated substances. Thus LiEt is roughly tetrameric in concentrated benzene solution, $MgEt_2$ is a viscous, non-volatile, insoluble liquid (Krause and v. Grosse, "Die Chemie der metall-organischen Verbindungen," Berlin, 1937), and $AlMe_3$ is found from vapour-density measurements (Laubengayer and Gilliam, *J. Amer. Chem. Soc.*, 1941, **63**, 477) to have a mean degree of polymerisation of 2 at 70°. The alkyls of Zn, Cd, Hg, B (Stock and Zeidler, *Ber.*, 1921, **54**, 531), Ga and In (Laubengayer and Gilliam, *loc. cit.*) are all monomeric in the vapour and in solution. The degree of polymerisation of $TlR_3$ does not appear to have been investigated.

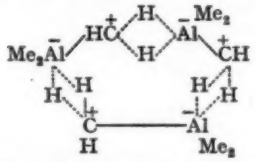
It is impossible to formulate such polymerisation in terms of normal valency bonds between the units in the polymer, since in each monomer all the valency electrons are engaged in covalent linkages. A possible explanation of the polymerisation is that it is due to dipole association; but this explanation will hardly account for the magnitude of the effect, which is greater than the association by hydrogen bonding of ammonia, water, and hydrogen fluoride.

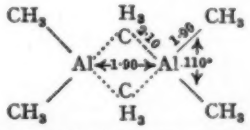
An attempt at solution of the problem has been made with $AlMe_3$ whose vapour density corresponds to the dimeric form at 70° (*idem, ibid.*). It is found (Davidson, Hugill, Skinner, and Sutton, *Trans. Faraday Soc.*, 1940, **26**, 1212; Brockway and Davidson, *J. Amer. Chem. Soc.*, 1941, **63**, 3287) that the electron-scattering curve fits that calculated for an ethane-like dimer in which the aluminium atoms are linked together. It is therefore supposed that some or all of the links have partial single-electron-link character and partial no-link character. Several difficulties at once present themselves. (*a*) The covalent radius of aluminium exceeds that of silicon; hence an Al–Al bond would be expected to be longer than an Si–Si bond, and an electron-deficient bond to be longer still. In fact, the Al–Al distance calculated according to the ethane-like model is considerably shorter (2·20A.) than the Si–Si distance (2·34A.) in $Si_2Me_6$. (*b*) The Raman spectrum of methyl-aluminium (Kohlrausch and Wagner, *Z. physikal. Chem.*, 1942, *B*, **52**, 185) resembles those of the aluminium halides much more than that of $C_2Cl_6$. (*c*) If the polymerisation is due to the formation of electron-deficient links between the central atoms in pairs, it seems strange that $BMe_3$ does not polymerise at all, whereas LiEt polymerises much more than two-fold.

Unfortunately, the experimental data on the alkyls are scanty, but those available can be satisfactorily interpreted in terms of the present theory, as will now be shown.

Methylaluminium has been studied in the most detail. The formula $Al_2Me_6$ has been proposed for the polymer on the basis of vapour-density determinations by Laubengayer and Gilliam (*loc. cit.*), and is consistent with the tensimetric measurements by Davidson and Brown (*J. Amer. Chem. Soc.*, 1942, **64**, 318) on mixtures of $AlMe_3$ and $BMe_3$. However, the evidence as published by no means excludes the possibility that methylaluminium is a mixture of polymers. The hypothetical trimer (XII), for instance, gives as good agreement with the electron-diffraction evidence as the ethane-like dimer (the calculations were carried out by H. A. Skinner, and are to be published shortly); and whereas the latter raises extreme difficulties of formulation, the former is easily understood in terms of the protonated double bond. (The + and − signs indicate a formal displacement of an electron from the carbon to the aluminium atom.) Supposing, however, that the dimeric formula is correct, the ethane-like structure is not the only one compatible with the electron-diffraction evidence. As already mentioned, the low-frequency end of the Raman spectrum of $Al_2Me_6$ (Kohlrausch and Wagner, *loc. cit.*) is much more closely similar in structure to those of the aluminium halides than that of $C_2Cl_6$, which suggests a bridged structure for the dimer. Brockway and Davidson (*loc. cit.*) found that moderate agreement with the observed electron-diffraction curve was given by a bridged structure with the dimensions shown in

(XII.)



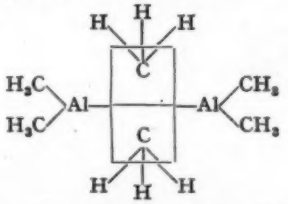



(XIII.)

(XIII). They rejected such a structure on the ground that the Al–Al distance was much too short for non-bonded atoms; but this objection is not final, for reasons that will now be given.

If we suppose that the central ring in $Al_2Me_6$ (XIII) is similar in electronic structure to that in $B_2H_6$, then we may write the structure of the former as in (XIV). Here a line between atoms denotes an ordinary $\sigma$ bond,

(XIV.)



and the rectangle represents a $\pi$ bond between the aluminium atoms, its lobes overlapping the fourth valency orbitals of the central carbon atoms. We may thus emulate Pitzer (*loc. cit.*) and speak of a " methylated double bond " between the aluminium atoms. According to this interpretation, one would expect the Al–Al distance to be between that of a single bond and that of a double bond, and this is what is observed. The other dimensions found for the molecule are quite consistent with this idea. However, further speculation on the structure of the alkyls in general must await more definite information on the molecular complexity of aluminium alkyl or other alkyls.

The author is indebted to Mr. R. P. Bell for much helpful discussion and criticism.

BALLIOL COLLEGE, OXFORD. [*Received, October 4th*, 1945.]

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# NOTES.

*The Preparation of Halogenated Methoxybenzaldehydes and the Demethylation of the Corresponding Benzil Derivatives.* By HARRY SHAPIRO and KENNETH A. SMITH.

5-BROMO-2-METHOXYBENZALDEHYDE may be prepared most conveniently by the methylation of 5-bromosalicylaldehyde in acetone solution by dimethyl sulphate and a suitable metal carbonate. 5-Bromosalicylaldehyde (Auwers and Bürger, *Ber.*, 1904, **37**, 3934) is simpler to obtain as a starting material than 2-methoxybenzaldehyde, which may be brominated directly (Perkin, *Annalen*, 1868, **145**, 304). The demethylation of 5 : 5′-dibromo-2 : 2′-dihydroxybenzil described by Kuhn, Moller, and Went (*Ber.*, 1943, **76**, 900) is not practicable for amounts larger than 2 g. A modification of their process using chlorobenzene as a solvent gives excellent yields.

Both the methylation and demethylation procedure is applicable to the corresponding 5-chloro- and 3 : 5-dichloro-compounds.

*5-Bromo-2-methoxybenzaldehyde.* 5-Bromosalicylaldehyde (12·6 g.) is dissolved in acetone (100 c.c.) in which is suspended anhydrous potassium carbonate (7 g.). Dimethyl sulphate (12·6 g.) is added and the mixture is refluxed with stirring for 2 hours on the water-bath. The solvent is removed from the colourless solution and the residue treated with hot water (150 c.c.). After cooling, the colourless crystalline *compound* is separated, washed with 2N-NaOH and then with water until the washings are neutral. The product is then dried at 70° (13·4 g., 99·3%), m. p. 116·4° (corr.) (Found : C, 44·8; H, 3·5; Br, 37·5; MeO, 14·6. $C_8H_7O_2Br$ requires C, 44·7; H, 3·3; Br, 37·2; MeO, 14·4%).

*5 : 5′-Dibromo-2 : 2′-dihydroxybenzil.* 5 : 5′-Dibromo-2 : 2′-dimethoxybenzil (21·4 g.) is dissolved in dry chlorobenzene (100 c.c.) to which is added powdered anhydrous aluminium chloride (214 g.). The mixture is stirred for 7 hours at 60° on a water-bath. The dark liquid is then poured into an equal volume of N-hydrochloric acid and the chlorobenzene removed by steam distillation. The dark residue is dissolved in 2N-NaOH (400 c.c.) and filtered from a small amount of insoluble material. On acidifying with concentrated hydrochloric acid (Congo red), the canary yellow demethylated *product* is obtained. This is collected, washed with water and dried at 90° (19·2 g., 96%). After crystallis-

ation from alcohol or glacial acetic acid, it has m. p. 214° (corr.) (Found: C, 42·0; H, 2·0; Br, 39·9. $C_{14}H_8O_4Br_2$ requires C, 42·0; H, 2·0; Br, 40·0%).—RESEARCH DIVISION, BAYER PRODUCTS, LONDON. [*Received, November 23rd*, 1945.]

*Chloromethylation of* 1- *and* 2-*Chloronaphthalenes.* By DENIS H. S. HORN and FRANK L. WARREN.

VARIOUS methods, designed to increase the yield, have been described for the chloromethylation of aromatic nuclei. We have been unable to confirm the 90% conversion reported by Darzens and Levy (*Compt. rend.*, 1936, **202**, 73; cf. Grummit and Buck, *J. Amer. Chem. Soc.*, 1943, **65**, 295). The essential details—without which, the yield is reduced by more than 50%—of any method seem to be the removal of acids and the drying of the crude product with anhydrous potassium carbonate prior to distillation as recommended by Grummit and Buck (*loc. cit.*).

The chloromethylation of 1-chloronaphthalene gave 1-*chloro*-4-*chloromethylnaphthalene*, m. p. 78—79°, which was oxidised by dilute nitric acid (cf. Weissgerber and Kurber, *Ber.*, 1919, **52B**, 346) to 4-chloro-1-naphthoic acid, m. p. 221—223°, identical with that of the acid synthesised from 1-chloro-4-bromonaphthalene, although Friedlander and Weisberg (*Ber.*, 1895, **28**, 1843) give m. p. 210°.

The chloromethylation of 2-chloronaphthalene gave a mixture of difficultly separable isomers. Catalytic hydrogenation experiments in the presence of palladium black on calcium carbonate (Busch and Stöve, *Ber.*, 1916, **49**, 1063) caused the reduction of the alkyl-chlorine without the elimination of the halogen attached to the nucleus, and the velocity of the reaction indicated a break in the curve when 85% of the hydrogen had been absorbed. By stopping the reduction at 60—67% absorption and distilling the product, 2-*chloro*-1-*chloromethylnaphthalene*, m. p. 67—68°, was separated. Amination of the reduction product, 2-chloro-1-methylnaphthalene, and acetylation gave an acetyl derivative, m. p. 188—189°, recorded by Fries and Hubner (*Ber.*, 1906, **39**, 444) for 1-methyl-2-acetnaphthalide, but the yield was too small for analysis. The structure was confirmed by oxidation to 2-chloro-1-naphthoic acid; the slow rate of catalytic reduction may be explained by steric hindrance. The other isomer, 7-*chloro*-1-*chloromethylnaphthalene*, m. p. 75°, was obtained by crystallisation of the mixture from ligroin. The structure was established by direct oxidation with dilute nitric acid, or *via* 7-*chloro*-1-*hydroxymethylnaphthalene*, to 7-*chloro*-1-*naphthoic acid*, synthesised from 7-chloro-1-bromonaphthalene, m. p. 67°. This latter compound has been designated as 6(or 7)-chloro-1-bromonaphthalene by Guareschi (*Jahrb. Fortsch. Chemie*, 1888, 921); but the acid, m. p. 238—240°, obtained from it by the Grignard reaction, and its p-*bromophenacyl ester*, m. p. 144—145°, are different respectively from 6-chloro-1-naphthoic acid, m. p. 189° [synthesised by the method of Price *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 1861)] and its p-*bromophenacyl ester*, m. p. 142—143°.

*Chloromethylation of* 1- *and* 2-*Chloronaphthalenes.*—Dry hydrogen chloride was passed to saturation into a suspension of paraformaldehyde (12·5 g., 0·14 mol.) in glacial acetic acid (80 ml.) at room temperature and finally at 0°; the chloronaphthalene (40·6 g., 0·25 mol.) and syrupy phosphoric acid (20 ml.; *d* 1·72) were added and the mixture rapidly stirred and kept at 95° for 10 hours and then poured into water, the oil washed with 5% sodium carbonate and water, taken up in ether and dried with potassium carbonate. The solvent was removed and the product distilled under reduced pressure.

(*a*) 1-Chloronaphthalene gave unchanged material (11 g., b. p. 115—140°/2 mm.) and a fraction (12 g., b. p. 140—180°/2 mm.) which redistilled at 145—158°/0·5 mm. to give a solid which, crystallised twice from ligroin and then from methanol, gave 1-*chloro*-4-*chloromethylnaphthalene* as transparent needles, m. p. 78—79° (Found: Cl, 33·5. $C_{11}H_8Cl_2$ requires Cl, 33·7%).

(*b*) 2-Chloronaphthalene gave unchanged material (10·5 g., b. p. 110—130°/1·5 mm.) and a fraction (26·3 g., b. p. 130—170°/2 mm.) which redistilled at 195—198°/10 mm. (Found: Cl, 33·2%) to give a mixture of isomeric chlorochloromethylnaphthalenes. (i) Crystallisation from a large volume of ligroin gave needles of 7-*chloro*-1-*chloromethylnaphthalene*, m. p. 75° (yield 5 g.) (Found: Cl, 33·2%); but an isomer was not obtained by fractional crystallisation. (ii) Freshly distilled isomeric mixture (20 g.) in alcohol (300 ml.) containing 10% alcoholic potash (60 ml.) and palladium black on calcium carbonate (2 g.), prepared according to Busch and Stöve (*loc. cit.*), was shaken with hydrogen until 60% of the theoretical had been absorbed. The reaction mixture was poured into water, the oil dissolved in ether and dried over sodium sulphate. The oil obtained by the removal of the solvent gave 7-*chloro*-1-*methylnaphthalene* as a mobile oil (13 g.), b. p. 158—170°/10 mm. (Found: Cl, 20·6. $C_{11}H_9Cl$ requires Cl, 20·1%), and a solid (4·5 g.), m. p. 46°, b. p. 186—194°/10 mm., which twice crystallised from ethanol gave colourless needles (2 g.) of 2-*chloro*-1-*chloromethylnaphthalene* (2 g.), m. p. 67—68° (Found: Cl, 33·5%).

7-*Chloro*-1-*hydroxymethylnaphthalene.*—7-Chloro-1-chloromethylnaphthalene (0·5 g.), potassium carbonate (0·3 g.), water (25 ml.), and benzene were refluxed for 8 hours and the benzene evaporated. The crystals, which separated on cooling, recrystallised from water to give 7-*chloro*-1-*hydroxymethylnaphthalene* as large plates, m. p. 101·5—103° (Found: Cl, 18·2. $C_{11}H_9OCl$ requires Cl, 18·4%).

p-*Bromophenacyl Ester of* 4-*Chloro*-1-*naphthoic Acid.*—1-Chloro-4-chloromethylnaphthalene (2 g.) was refluxed with water (187 ml.), nitric acid (15 ml.), dioxan (20 ml.), and benzene (5 ml.) for 48 hours. The acid, isolated from the unoxidised material, was crystallised twice from aqueous dioxan to give 4-chloro-1-naphthoic acid (0·4 g.) as long needles, m. p. 221—223° (Found: Cl, 17·8; Eq. Wt., 206·8. Calc. for $C_{11}H_7O_2Cl$: Cl, 17·2%; Eq. Wt., 206·5). The p-*bromophenacyl ester* crystallised from alcohol in soft needles, m. p. 130—131° (Found: C, 56·6; H, 3·2. $C_{19}H_{12}O_3ClBr$ requires C, 56·5; H, 3·0%). Mixed m. ps. of both acid and ester with authentic specimens (below) showed no depression. The acid was synthesised from 1-chloro-4-bromonaphthalene (2·5 g., b. p. 150—156°/0·7 mm., m. p. 66·5—67·5°) by the Grignard reaction, as described for 1-bromonaphthalene by Gilman, St. John, and Schulz (*Org. Syn.*, 1931, **11**, 80), and crystallised from ethanol to give 4-chloro-1-naphthoic acid (1·1 g., m. p. 221—223°) (Friedlander and Weisberg, *Ber.*, 1895, **28**, 1843, give m. p. 210°) (Found: Cl, 17·9%; Eq. Wt., 208·3). The *p*-bromophenacyl ester had m. p. 130·5—131° (Found: C, 56·2; H, 3·1%).

2-Chloro-1-chloromethylnaphthalene (0·5 g.) was refluxed with water (50 ml.) and nitric acid (4 ml.) for 15 days to give a small quantity of acid, which after distillation under reduced pressure had m. p. 151°. Rabe (*Ber.*, 1889, **22**, 394) gives 2-chloro-1-naphthoic acid, m. p. 150—152°.

7-*Chloro*-1-*naphthoic Acid.*—2-Chloro-8-chloromethylnaphthalene (1 g.) was refluxed with water (100 ml.) and nitric acid (8 ml.) for 24 hours. The acid was separated from unchanged material and crystallised from toluene to give soft needles of 7-*chloro*-1-*naphthoic acid* (0·36 g.), m. p. 235° (Found: Cl, 17·3; Eq. Wt., 203·4. $C_{11}H_7O_2Cl$ requires Cl, 17·2%; Eq. Wt., 206·5). Its p-*bromophenacyl ester* crystallised from alcohol in soft needles, m. p. 145—146° (Found: C, 56·3; H, 3·0%). Mixed m. p.s of both acid and ester with authentic specimens showed no depression. The acid was synthesised from 7-chloro-1-bromonaphthalene (cf. Gilman, St. John, and Schulz, *loc. cit.*) to give 7-chloro-1-naphthoic acid, m. p. 238—240° (Found: Cl, 17·5%; Eq. Wt., 205·8). Its *p*-bromophenacyl ester had m. p. 144—145° (Found: C, 56·2; H, 3·1%).

6-Chloro-1-naphthoic acid, prepared by the method of Price *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 1861), had m. p. 188—189°. Its *p*-bromophenacyl ester crystallised from alcohol as soft needles, m. p. 142—143° (Found: C, 56·5; H, 3·1%).

M. ps. are corrected.—NATAL UNIVERSITY COLLEGE (UNIVERSITY OF SOUTH AFRICA), PIETERMARITZBURG, NATAL. [*Received, November 23rd*, 1945.]

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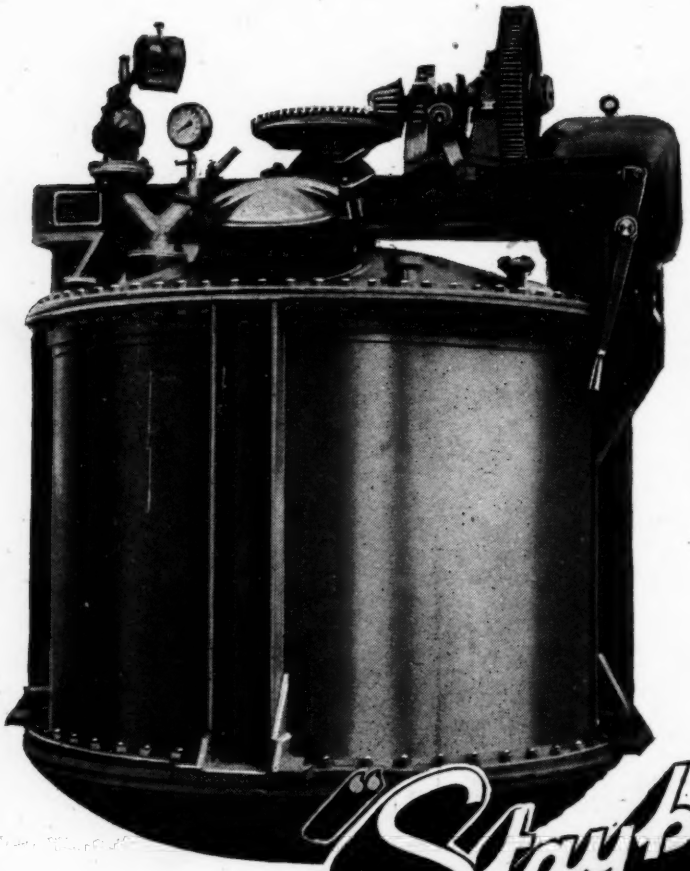

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